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INTRAFAMILIAL AND INTERFAMILIAL SPREAD OF LIVING VACCINE STRAINS OF POLIOVIRUSES

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Fifty-six household units participated in a study of the spread of poliovirus within families and between families. Within this group all persons above the age of 6 months and not naturally immune had previously received the Salk vaccine. Each of the families used included at least three naturally susceptible members. Sabin vaccine was administered by squirting 1 ml. of the single-strain virus suspension into the back of the recipient's mouth. All but one adult was successfully infected after receiving the recommended dose. Virologic and serologic methods demonstrated transmission to many contacts, fecal excretion of the virus being the most sensitive indicator of that fact. The virus commonly appeared in the pharyngeal secretion within the first two days. The most important factor favoring intrafamilial transmission was low socioeconomic status. No evidence was found to suggest that any illness, however minor, followed the administration or spread of any of the three vaccine virus strains used.

WITH the isolation, selection, purification, and large-scale production by Koprowski,[1] Sabin,[2] and Roca-Garcia and others [3] of attenuated variants of polioviruses of all three types, we are offered the opportunity to substitute live-virus vaccination against poliomyelitis for the formalin-inactivated vaccine in current use.

Among the generally accepted advantages of vaccination with the infectious strains we may list (1) the ease of administration: oral versus parenteral administration; (2) the duration of protection: theoretically life-long; (3) the percentage of effectiveness: perhaps close to 100% versus the 70 to 80% now attained by Salk vaccine; (4) the rapidity of effective immunization: making possible its use in established epidemics; and (5) the "herd" immunity produced: by inducing local intestinal resistance. The generally recognized disadvantages include (1) the necessity for an interval of some weeks between the administration of the different types and (2) the danger of accidental contamination of the vaccine by other living microbial material. The latter danger can be obviated by proper care during production and safety testing afterward, and the former may be overcome by future technical development.

A controversial characteristic of live-virus poliomyelitis vaccination is the ability of these strains to be transmitted from the vaccinated person to his

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contacts. The very earliest work with living attenuated polioviruses showed that, some days after oral administration, they are excreted in the feces. Subsequently, Koprowski and others,[4] Dick and others,[5] Horstmann,[6] Martins da Silva and others,[7] Smorodintsev,[8] Sabin,[9] and Gard,[10] using various strains of all three types, have unequivocally demonstrated spread to susceptible persons under various conditions of contact. In itself, the occurrence of this phenomenon probably would be of little concern, were it not for the possibility that the fecally excreted viruses being spread may have undergone back-mutation to a level of neurovirulence greater than was acceptable in the original oral vaccine. One might well take the even more extreme position that, were it not for this possibility of back-mutation, spread of vaccine viruses by contagion is a decided advantage of live-virus vaccination, in that the administration of vaccine to only a portion of the population might result in the effective vaccination of the entire population. This would be vaccine-induced "herd protection" of a level not yet achieved with any immunizing agent.

The demonstrated tendency of attenuated strains of poliovirus to change in the direction of increased virulence on multiplication in the intestinal tract may have little practical significance in human beings, but a final conclusion is as yet unwarranted. Intraneural tests of the excreted viruses have yielded inconsistent results in the hands of different investigators and, moreover, no one has ventured to suggest what the maximum tolerable reversion might be. Regardless of the eventual result of this disagreement, knowledge of the infectivity and transmissibility of the vaccine strains is essential to their rational use in field trials and, eventually, in routine practice. The present communication will report, in preliminary fashion, the results of studies on the capacity of a set of vaccine strains to spread within families living under normal conditions in southern Louisiana.

Material and Methods

Population Studied.—Families for the present investigation were recruited in 1958 from a group in New Orleans which had been under our observation from 1953 through 1957 in a study of natural infection with polioviruses.[11] Their infection history was therefore unusually well known. During 1956 and 1957 all persons above the age of 6 months and not naturally immune to all three poliovirus types had been given three suitably spaced inoculations with Salk vaccine. Infants who were under 6 months of age at the beginning of this study were not vaccinated after it began.

To be eligible for the present purpose, a family had to include, for any given type, at least three "naturally susceptible" members, defined as persons without prior natural homologous infection as observed by us and coupled with the complete absence of naturally acquired serum-neutralizing antibody as measured by the direct cytopathic test. On this basis, a family might be "eligible" for more than one type, and many were used two or three times. Each feeding and family observation was therefore designated as a separate "unit" and so reported below. In addition, in several instances the same virus type was fed more than once in a single household when the first failed to cause infection and/or spread. Again, each feeding was considered a separate unit of study. On a few occasions, the vaccine was purposefully fed to naturally immune persons in households which also contained two homologously susceptible persons as indicators of spread. These units are separately considered. Family units were assigned to one of three socioeconomic categories: Caucasian–upper economic, Caucasian–lower economic, and Negro. The Caucasian group was divided on the basis of an aggregate family income of $3,500 per year (in 1953), and all Negro families fell below this level. Although arbitrary, this economic division was rather well correlated with social and sanitary facilities and practices such as household crowding, adequacy of toilet and hand-washing equipment, and "personal hygiene." Since there has been no prior evidence that race as such plays any part in the transmission of polioviruses, units usually are combined below only as upper economic or lower economic.

Virus Strains and Vaccine Administration.—The viruses used were kindly provided by Dr. Albert Sabin and were from single large pools of each type that had fulfilled his rigid criteria for purity and attenuation.[2] These strains were designated L Sc, 2 ab (type 1), P 712, Ch 2 ab (type 2), and Leon 12 a_1b (type 3). The stock material, undiluted or diluted as necessary with Hank's balanced salt solution, was distributed in 1.2-ml. aliquots into individual screw-topped vials, which were then kept at −20 C until used. The doses fed were calculated to contain approximately 100,000 (5 log doses) or 10,000,000 (7 log doses) infectious particles. Repeated titration of sample vials in cultures of rhesus kidney cells showed that actually an average of 5.3 and 7.3 log doses (type 1) and 5.1 and 7.1 log doses (types 2 and 3) had been used although, by error, a few persons received 3.6 log doses (4,000 infectious units) early in the study. These figures may need some upward revision for, in a recent communication, Sabin [9] reports that higher titers of his vaccine pools may be obtained by titration in cynomologous kidney-cell tissue cultures and an improved technique. Consequently, the doses we used may have been greater than reported here, i. e., approximately 4.3, 6.0, and 8.0 log doses (type 1), 5.3 and 7.3 log doses (type 2), and 3.9, 5.4, and 7.4 log doses (type 3).

Administration of the Sabin vaccine was done in the recipients' homes by one of us (D. R. L.) by squirting 1 ml. of the single-strain virus suspension into the back of their mouths, after which they drank a glass of water. The vials of vaccine were carried into the field on ice, and were never used for more than six hours from the time of leaving the laboratory. Several titrations of vials returned to the laboratory after that time showed that no significant titer decline had occurred. Individual medicine droppers were used in administration, and extreme care was taken to prevent contamination of the skin of the recipient or of objects in the home.

Method of Study and Collection of Specimens.—For each family unit of study, one susceptible person was chosen for administration of the homologous type of vaccine virus and was designated the "index" person. The two or more other susceptible persons and the naturally immune household members were all observed as "family contacts." In a few instances, observations were made on the

During the investigation of a number of family units, an attempt was made to detect the presence of poliovirus on the skin of the hands and buttocks of some children, and on the floor, on toys, and on other fomites. For this purpose, cotton pledgets wetted with Hank's solution were swabbed over the appropriate surface and returned to the laboratory, where they were squeezed almost dry. The resulting fluid was treated as indicated below for fecal extracts and pharyngeal gargles.

Laboratory Procedures.—Rhesus monkey kidney-cell tissue cultures, prepared in this laboratory, were employed throughout, with use of techniques now standard.[11]

For virus isolation, stool specimens were processed into 10 to 20% fecal extracts containing penicillin, streptomycin, and nystatin (Mycostatin), while pharyngeal specimens were used as collected, after centrifugation and the addition of antibiotics. Each of four tissue-culture tubes was inoculated with 0.25 ml. of each specimen. The latter were

TABLE 1.—*Schedules of Specimen Collection*

Donors	Type of Specimen	Days After Vaccine Feeding on Which Indicated Specimens Were Collected		
		Complete Schedule	Modified Schedule	Abbreviated Schedule
Index person	Blood	0, 3, 7, 11, 14, 18, 21, 60	0, 8, 20, 60	0, 60
	Pharyngeal	0-14	0, 2, 4, 8	None
	Fecal	0-14, 18, 21, 25, 28; 1 x per wk. to termination	0, 2, 4, 8; 1 x per wk. to termination	0; 1-2 x per wk. for variable period
Family contacts	Blood	0, 60	0, 20, 60	
	Pharyngeal	3-17	0	
	Fecal	0, 3-17, 21, 25, 28, 31; 1 x per wk. to termination	Same as index	Same as index
Extra-household contacts	Blood	0, 60	None	None
	Fecal	7, 14, 21		
No. of household units completed by indicated schedule		26	17	8 (plus 5 immune feedings)

possible spread of these viruses to other persons not living in the same domicile who are referred to as "extra-household" contacts.

The various schedules of specimen collection are outlined in table 1. Day "0" is the day of feeding in all instances. These schedules were set up as guides only and were often modified to suit the individual situations found in many households.

Blood specimens were almost always collected by venipuncture, with use of vacuum bleeding tubes; less than 1% were by heel puncture in small infants. Pharyngeal specimens were obtained from adults and older children by gargling. Screw-topped ointment jars were prepared with 7 ml. of tissue-culture maintenance fluid; this provided the gargle fluid, and it was expectorated back into the same container. With small children, the tonsillar area and posterior pharynx were thoroughly swabbed with a dry cotton-tipped applicator, and the latter was then dropped into a tube containing 5 ml. of maintenance fluid. Fecal specimens consisted of a pellet of whole feces placed into an ointment jar. Specimens were held at refrigerator temperature, usually no longer than overnight, before processing in the laboratory.

incubated at 37 C and examined at intervals for 10 to 13 days, with a change of lactalbumin maintenance medium fluid on the fourth to seventh day. Specimens were recorded as negative if there was no evidence of a cytopathic effect after this time; if doubtful, the supernatants were pooled, and a subculture was made by inoculating 0.1 ml. of the pooled material into each of two new tubes which were then incubated for four to seven days. When a cytopathogenic agent was recovered, identification was first attempted by neutralization with hyperimmune rabbit antiserum prepared against the virus of the type fed. If complete neutralization did not occur, further investigation was made with the use of polyvalent serums against the other types of polioviruses, Coxsackie viruses A9 and B1-5, and ECHO types 1 to 14, followed by the appropriate monotypic tests.

Serums were tested for the presence of neutralizing antibody in the direct cytopathic test for the high-avidity antibody of Sabin.[8] Aliquots of each serum dilution were incubated for one hour at room temperature, with an equal quantity of virus suspension calculated to contain approximately 100 tissue culture infective doses ($TCID_{50}$) per 0.1 ml. For index persons, four tubes were used per two-

fold dilution and for contact persons, two tubes per twofold dilution. End-points are expressed as of the final serum dilution.

Results

The available data relating to 56 family units are the subject of this preliminary report. In 51 units, a naturally susceptible person was fed, the distribution of these by socioeconomic and family status being as follows: Negro, 13 children only; Caucasion–lower economic, 13 children only; and Caucasian–upper economic, 18 children and 7 parents. In five additional units, a homologously naturally immune index person was fed.

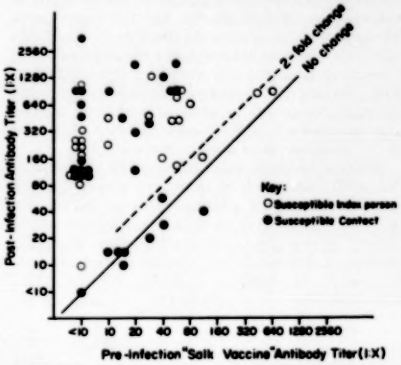
Infections in Susceptible "Index" Persons.—Of the 51 feedings represented by these household units, all but five resulted in the infection of the index person, as indicated by the subsequent recovery of homologous virus from the pharyngeal

TABLE 2.—*Summary of Efforts to Recover Virus from Pharynges and Feces of Index Persons Fed "Sabin Vaccine," by Virus Type, Dose, and Family Status*

Vaccine Virus, Type	Dose Fed, Log	Family Status	Homologous Virus Detected in Appropriately Collected Specimens: Pharyngeal, No. of Persons Examined	Pharyngeal, No. of Persons Positive	Fecal, No. of Persons Examined	Fecal, No. of Persons Positive
1	3.6	Child (2-8 yr.)	3	0	3	0
		Adult	1	0	1	0
	5.3	Child (2-8 yr.)	4	1	6	6
		Adult	2	0	2	1
	7.3	Child (2-5 yr.)	6	5	6	6
		Adult	1	1	2	2
2	5.1	Child (2-6 yr.)	5	0	6	6
		Adult	0	—	0	—
	7.1	Child (2-6 yr.)	7	4	8	8
		Adult	1	1	1	1
3	3.6	Child (1-2 yr.)	2	0	2	2
		Adult	0	—	0	—
	5.1	Child (3-7 yr.)	5	0	6	6
		Adult	0	—	0	—
	7.1	Child (2-6 yr.)	6	5	7	7
		Adult	1	0	1	1

and/or fecal excretions. As may be seen in detail in table 2, four of these failures were in persons who had received the small 3.6 log dose of type 1 vaccine. One of the four failures was an adult, who was then refed with 5.3 log doses of the same virus type. Again he failed to become infected, representing the fifth and last feeding failure. He was refed once more, with 7.3 log doses of the same type, and thereupon excreted virus fecally for five days.

Among the 46 persons who did become infected, fecal excretion was the most sensitive indicator of that fact. Pharyngeal excretion was usually detected after the administration of 7.1 to 7.3 log doses (16 of 22 persons examined), but was found after 5.1 to 5.3 log doses in only 1 of 16 persons examined. The serologic detection of infection, as indicated by a titer rise fourfold or greater, was even less reliable. Study of appropriate specimens of all persons is not yet complete, but as indicated in the figure, significant rises above the titers persisting from Salk vaccination completed one to two years previously often failed to occur where the titer before infection was greater than 1:40. It must also be added that in no instance did a significant serologic titer rise occur in any person from whose fecal specimens we failed to isolate virus. It may



Homologous antibody titers before and after proved infection with "Sabin vaccine" in naturally susceptible persons.

also be seen in table 2 that the age of the index person did not appear to affect the likelihood of infection after feeding with any given virus type or dose.

The duration of excretion was very variable; demonstrable excretion from the pharynx lasted from a minimum of 2 to a maximum of 17 days and,

TABLE 3.—*Duration of Pharyngeal and Fecal Excretion of Polioviruses After Oral Administration of "Sabin Vaccine"*

Observed Duration of Excretion, Days	No. of Persons with Indicated Duration After Ingestion of Indicated Virus Type: Type 1, Pharyngeal	Type 1, Fecal	Type 2, Pharyngeal	Type 2, Fecal	Type 3, Pharyngeal	Type 3, Fecal
1	0	0	0	0	0	0
2	0	1	1	0	0	0
3	0	0	1	0	0	0
4	1	0	0	0	0	0
5	0	1	0	0	0	1
6–10	4	4	5	5	3	0
11–15	1	1	0	1	1	2
16–20	1	3	0	2	1	2
21–30	0	2	0	2	0	3
31–40	0	2	0	3	0	3
41+	0	1	0	2	0	5
Mean duration	8.8	21.7	4.8	24.9	10.1	34.5
Mean interval*	1.9	4.8	1.8	5.3	1.8	4.2

* Average time elapsed between last negative specimen before excretion began and last positive and first negative specimen after excretion ended.

in the feces, from a minimum of 2 to a maximum of at least 137 days. There appeared to be no relationship between this duration and either the size of the infecting dose or the age of the recipient. Table 3 shows the distributions and means of the durations

of excretion after ingestion of the three virus types of vaccine. (The means of the intervals between the last negative specimen before excretion began and the last positive and the first negative after it ended are given to show the equivalence of the observations.) There is a suggestion that the excretion of type 3 virus may last longer than that of the other types, although the record in this series, 137 days with no end-point being reached, was with type 1.

The incubation period of infection, as measured by the interval between the ingestion of vaccine and the onset of continuous excretion of homologous virus, was very short in the majority of index persons on whom daily observations were made. Of 11 persons in whom pharyngeal excretion was systematically sought, three were excreting virus within one day, six by the end of the second day, and in only one each was excretion first detected on the third and fifth day respectively. Of 27 persons examined daily for the presence of virus in the feces, 17 were found to be excreting within one day, nine others by the end of the second day, and in only one was onset delayed until the fifth day. There was no suggestion of a relation to virus type or dose.

Complete series of blood specimens were collected from 16 of the susceptible index persons on days 0, 3, 7, 10, 14, 17, 20, and 60. Rise in neutralizing antibody titer, observed in 15 of these susceptible index persons, occurred between the 7th and 10th days in 12 instances, and between days 3 and 7 or 10 and 14 in two and one cases respectively. The antibody titer had clearly begun to decline between days 20 and 60 in 10 of these 15 persons.

Two susceptible index feedings are worth noting in detail. Reference has already been made to an adult who failed to become infected after ingesting 3.6 and 5.3 log doses of type 1 Sabin vaccine, but then excreted virus in the feces for five days after the administration of 7.3 log doses. It was felt that this man may have been naturally immune without demonstrable neutralizing antibody. One child was also fed more than once. After ingestion of a 3.6-log dose of type 3 Sabin vaccine, she had five days of fecal excretion but no serologic response. She was refed with a 5.1-log dose of the same type, whereupon she excreted for 29 days and experienced a marked rise in antibody titer from 1:56 to 1:800. The first infection in this child may represent the implantation of virus in so limited an area of the intestine that full evolution of the infection did not occur, and the antigenic stimulus thus was too weak. Thereafter, she remained fully susceptible, and acted as a nonimmune person on reexposure.

Infection Attempts in Naturally Immune Index Persons.—Only five naturally immune persons have so far been completely studied after ingestion of Sabin vaccine. Three of these were fed type 1 virus, and each of the others was fed type 2 or 3. All were children, and all were fed the larger dose. Three of the five failed to become reinfected. One child excreted type 1 virus in the feces for nine days, but failed to excrete from the pharynx; the child fed type 2 virus also excreted fecally for nine days, but no pharyngeal specimens were collected. Serums have not yet been tested.

Spread of Infection from the Index Person to Family Contacts.—Because of the large number of variables, any or all of which may significantly influence the spread of vaccine viruses within household units, the combination of units with identifiable differences is not fully justified. Table 4, therefore, reports the ratio of infections among naturally susceptible and naturally immune family contacts within the few units included in each category as defined by virus type, presence or absence of pharyngeal virus excretion, economic status, and family status of the index person. Since the dose of attenuated virus fed was not demonstrated to have an effect in the infected index person other than determining the likelihood of the occurrence of pharyngeal excretion, distribution of the results by dose was not tabulated. The determination of contact infection was based, in all cases, on the occurrence of fecal excretion.

TABLE 4.—*Homologous Infections Occurring Among Family Contacts of Index Persons Infected After Oral Administration of "Sabin Vaccine"*

Natural Immunity Status of Family Contacts	Family Status of Index Person	Virus Type	Contacts in Upper Economic Family Group: Occurrence of Pharyngeal Virus Excretion in Index Person: Yes — No. of Units	Yes — Ratio* of Contact Infections	No — No. of Units	No — Ratio* of Contact Infections	Contacts in Lower Economic Family Group: Occurrence of Pharyngeal Virus Excretion in Index Person: Yes — No. of Units	Yes — Ratio* of Contact Infections	No — No. of Units	No — Ratio* of Contact Infections
Susceptible	Child	1	4	2/9	3	1/6	2	2/6	3	2/9
		2	1	0/2	2	0/5	4	9/11	9	3/22
		3	1	0/2	5	1/20	5	13/15	4	7/11
	Parent	1	2	0/5	1	0/3	—	——	—	——
		2	1	0/3	—	——	—	——	—	——
		3	—	——	1	0/3	—	——	—	——
Immune	Child	1	4	2/8	3	1/7	2	1/6	3	1/6
		2	1	0/2	2	0/9	4	3/14	8	3/17
		3	1	0/3	5	0/6	5	9/21	4	2/11
	Parent	1	2	0/2	1	0/1	—	——	—	——
		2	1	0/1	—	——	—	——	—	——
		3	—	——	1	0/1	—	——	—	——

* Ratio of persons infected (numerator) to family contacts present in home (denominator).

Examination of this table shows a number of interesting contrasts. Among the susceptible family contacts of infected index children, many infections occurred, but there was a marked difference based on economic status, the families from the lower economic group experiencing many more. Among the three virus types of the Sabin vaccine, type 3 feedings appeared to have resulted in more spread. The presence of pharyngeal excretion may have been associated with more extensive spread than occurred in its absence, at least with types 2 and 3 virus, although a number of these contact infections apparently took place long after pharyngeal excretion had ceased. Despite the fact that the observations were few in number and restricted to families from the upper economic group, it is striking that no single instance of spread followed the infection of an index adult, even though several experienced prolonged pharyngeal excretion. Finally, the rather large number of reinfections among naturally immune persons is notable.

TABLE 5.—*Summary of Homologous Infections Occurring Among Family Contacts of Infected Index Children, by Economic Status and Virus Type*

Virus Type	Upper Economic Family Group		Lower Economic Family Group	
	Ratio* of Contact Infections	% of Contact Infections	Ratio* of Contact Infections	% of Contact Infections
Susceptible Contacts				
1	3/15	20	7/15	47
2	0/7	0	12/33	36
3	1/22	5	20/26	77
All	4/44	9	39/74	53
Immune Contacts				
1	3/15	20	2/12	17
2	0/4	0	6/31	19
3	0/9	0	11/33	33
All	3/28	11	19/76	25

* As in table 4.

Since differences based on economic status and virus type appeared to have been the most significant, a summary of homologous infections among the contacts of index children is shown in table 5. With the larger numbers of subjects now available, the "benefit" of lower economic status and the generally greater infectiousness of type 3 vaccine are more evident. Type 2 appears to have been the least infectious. No family contact infections resulted from the two successful feedings in naturally immune persons with types 1 and 2 viruses respectively.

The less frequent collection of stool specimens from contacts renders difficult exact statements about the interval of time between the onset of viral excretion in the index person and that in his contacts. On several occasions, however, it was as short as one day, and on others not before one, two, or three weeks. It was particularly notable that viral excretion by naturally immune persons was often greatly delayed. The infection records of two typical families from the lower economic group are reproduced in table 6.

Spread of Infection of Extra-Household Contacts.—An adequate record of specimens from persons outside the home who were in contact with Sabin vaccine-infected families is available in connection with only four study units, since extra-household studies were initiated only where conditions for spread were likely to be optimal, i. e., with the administration of 7 log doses in lower economic families. In one of these units, neither the two siblings within the family nor the one susceptible extra-household child contact became infected with type 2 poliovirus, despite prolonged fecal excretion by the index child and frequent, intimate contact.

The second of the units studied was remarkable in that a single 2-hour period of contact, confined exclusively to the type 3–infected index child, resulted in the infection of two out of three child visitors. The third unit is in some contrast in that a similar two-hour contact period between three child visitors and the four infected children in the family studied resulted in only one infection. The two who missed infection had the same limited opportunity two weeks later and again escaped.

A special study was planned around a fourth unit which was intended to initiate a long series of passages from one household to another, among a group of cooperative, related families. The index child was fed type 3 Sabin vaccine and then removed from all play contact, except with her siblings; on infection of the four siblings, only the latter were permitted to associate with the extra-household families. The second link in the intended series was a large family containing five susceptible cousins. Unfortunately, this passage failed completely, despite frequent and intimate play contact, perhaps because of interference by coincidental natural episodes of ECHO type 1 and poliovirus type 2 involving four of the five type 3–susceptible children in the exposed household. However, three of the four other extra-household contacts in three households did contract infection with type 3.

Nature of the Infection Experienced by Contacts.—Only on a single occasion was homologous virus isolated from the pharyngeal specimen of a contact. The distributions and means of the durations of fecal homologous polioviral excretions, by contacts of persons ingesting Sabin vaccine, are indicated in table 7.

The significance of the shorter mean duration of type 1 excretion is doubtful, in view of the great variation among individuals and the small numbers involved. Of greater import is the rather large number of contact persons who excreted for very short periods of time, and who were therefore unlikely to be able to spread their infections to others. This is particularly characteristic of those naturally im-

mune, but is also true of a substantial proportion of the naturally susceptible contacts. Since all of the persons who excreted for only one day also failed to experience a booster rise in high-avidity antibody titer, and since, in many instances, fecal specimens were not obtained daily from contacts (table 6), it is quite likely that a number of contact infections with only brief viral excretion were missed. It is interesting, nevertheless, that the mean duration of excretion of all three types among susceptible contacts (24.3 days) was very close to the same mean among susceptible index persons (28.2 days).

The likelihood of detecting a titer rise after proved infection in those persons who had preexisting antibody derived from Salk vaccine was previously discussed and illustrated in the figure. The ence between these agents and attenuated strains being fed was strongly suggested. Table 8 gives three examples. In unit 10, Coxsackie B5 was infecting all three susceptible children at the time when type 1 Sabin vaccine was fed to the 5-year-old. The large dose administered may have suppressed further multiplication of the Coxsackie virus in the index child, but the smaller dose received by the others by way of "normal" contamination appears not to have been sufficient, and they escaped "vaccination." Unit 15 may illustrate reciprocal interference between a "wild" type 2 and the attenuated type 1 virus. At a later time, after both types had disappeared from the family, the index child became infected with type 2, perhaps from a neighborhood source outside the home. In unit 46, an ECHO

TABLE 6.—*Sample Families to Illustrate Spread of "Sabin Vaccine" After Administration to Single Naturally Susceptible Index Child**

Family Status	Age, Yr.	Homologous Natural Immunity Status†	Homologous Antibody Titer 1:x on Day 0	Homologous Antibody Titer 1:x on Day 62	Presence of Homologous Virus in Feces on Day 0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Unit 6: Negro, Index Fed 5.3 Log Dose of Type 1 Virus																			
Father	...	I	640	320	—	—	—		—		—		+	+		—			—
Mother	...	I	80	160	—		—		—				—	—	—				—
Children	12	S	28	20	—			—		—		—	—		—			—	—
	9	S	28	20	—	—		—		—	—				—			—	
	8	S	10	14	—		—	—		—			—	+			—		—
	7	S	20	320	—	—			—		+		+		+		+		
	5	S	<2	10	—	—		—			+	—		—			—		—
→	3	S	10	320	—	—‡		+			+	+		+			+	+	
	1	S	<2	640	—		—	—		—		—		+			+		+
Unit 39: Caucasian-Lower Economic, Index Fed 5.1 Log Dose of Type 3 Virus§																			
Father	...	I	20	14	—	—						—			+				
Mother	...	I	28	20	—	—				—		—			—				
Children	11	I	450	640	—		—			—		+		—			+	—	
	9	I	160	160	—		—	—		—		+	—		+				+
	6	S	5	110	—	—		—			+		+					+	
	5	S	<2	110	—	—	+			—	+	+	—				+		
→	3	S	<2	160	—	+‡	+			+	+			+			+		
	2	S	<2	110	—		+			—		+		+	+	+		+	

* "+" indicates virus isolation; "—" indicates no virus isolation from available specimens; and no symbol indicates no specimen collected. "Index" child indicated by arrow.
† I = immune; S = susceptible.
‡ No virus isolated from pharyngeal specimens collected on day 1 through 10.
§ On 13th day homologous poliovirus was isolated from kitchen floor.

more frequent absence of rise from low initial titer in infected contacts, as compared with infected index persons, is notable and related to the frequency of transient infections in the contacts. Among the 14 naturally immune persons in whom infection was observed and whose serums have been studied, no rise in titer could be demonstrated.

Coincidental "Wild" Enteroviral Infections.—Since many of the family units of study were being investigated during the summer and autumn months, and since New Orleans is an area of high enteroviral endemicity, it is not surprising that several episodes of infection with other enteric viruses occurred coincidentally with the administration of the Sabin vaccine: poliovirus type 2, ECHO virus types 1, 6, and 9, Coxsackie virus types A9 and B5, and an unidentified agent with adenovirus-like cytopathogenicity. On several occasions, interfertype 1 episode was either just beginning or nearing termination in the household when the index child was fed with attenuated type 3 Sabin vaccine. The ECHO infections spontaneously disappeared or were suppressed by the spreading attenuated poliovirus, and eventually all susceptible children became infected. In addition to other episodes similar to the above, many casual infections with enteroviruses, including an ECHO 9 isolation from a pharyngeal gargle, were detected later during the course of unit investigations, when interference could not be postulated.

Virus Recovery from the Skin and from Fomites in Households.—During the course of the investigation of 26 study units, some attempt was made to detect the presence of homologous poliovirus from sites other than the pharyngeal or fecal excretions during that period after vaccine administration

when the virus was circulating widely among family members. This effort was opportunistic, not carefully organized, and was made in those households with the poorest hygienic standards where the likelihood of environmental contamination was greatest. The places examined by swabbing included most commonly the skin of the hands, feet, and buttocks (excluding the perianal area) of an index child or his infected siblings, toys, floors, and doorknobs.

TABLE 7.—*Duration of Fecal Excretion of Homologous Polioviruses by Family Contacts of Persons Fed "Sabin Vaccine"*

Observed Duration of Excretion, Days	No. of Family Contact Persons					
	Immune			Susceptible		
	Type 1	Type 2	Type 3	Type 1	Type 2	Type 3
1	4	3	5	4	0	3
2	1	2	0	0	1	0
3	0	0	0	1	0	0
4	0	0	0	0	0	0
5	0	0	0	0	0	0
6-10	0	1	3	1	1	3
11-15	0	0	0	0	4	1
16-20	0	0	0	0	1	4
21-30	0	0	2	1	0	0
31-40	0	0	1	2	3	2
41+	0	0	0	1	2	6
Mean duration	1.2	2.7	9.8	16.0	27.0	27.0
Mean interval*	6.6	2.3	4.3	5.9	3.9	5.8

* As in table 3.

In five study units a poliovirus was recovered. In one instance the homologous type 2 was collected from the buttocks of the index child, and in two other instances the homologous type 3 was found on the buttocks of an infected sibling or on the kitchen floor. In a fourth unit, the homologous type 3 was recovered from the hands of the index child in four separate attempts on different days. The fifth instance is most interesting in that in a family fed Sabin vaccine type 1, which experienced a coincidental "wild" type 2 poliovirus infection, only the latter virus was found in a swab of the living room floor.

Illness Associated with Infection with Attenuated Vaccine Viruses.—Despite intensive and leading questioning, no evidence could be found to suggest that any illness, however minor, could be related to the infections produced by the administration or spread of the vaccine virus strains.

Comment

Although the primary object of this still-continuing investigation was the study of the transmission of infection with the attenuated poliovirus vaccine strains of Sabin, the results relative to primary infection in the vaccine recipient are of interest. With oral inocula consisting of approximately 100,000 infectious units, the dose recommended by Sabin for routine use, all of the three strains considered were able to initiate infection in all but one of the presumably susceptible persons. However, pharyngeal infection after administration of doses of this size was exceptional, in contrast to the usual appearance of virus in the throat after a larger inoculum containing somewhat more than 10 million viral particles. A dose of 4,000 units of type 1 virus failed to infect four persons to whom it was given, and an equal dose may have been on the border line of infectivity with type 3. All of the foregoing suggests that the infectivity of the attenuated strains must be considerably less than that of "wild" strains. This is consistent, moreover, with the greatly reduced intrafamilial dissemination of the attenuated strains, as compared with the results of studies of natural poliovirus infections with the same and similar families [11] in which more than 90% of susceptible persons became infected.

After infection in the recipient, however, the sequence of events, in terms of the duration of pharyngeal and fecal excretion of virus and of serologic response, greatly resembles that which follows natural infection in Salk-vaccinated persons. Unfortunately, titrations of virus in fecal extracts have not yet been made. The failure of many persons to manifest an antibody rise, especially if the preinfection titer derived from formalinized vaccine is greater than 1:40, should be re-emphasized, since this phenomenon renders invalid studies based exclusively on serologic examination. The rise in antibody titer, when it did occur, between the 7th and 10th day after ingestion in the majority of persons,

TABLE 8.—*Examples of Families Experiencing Episodes of Natural "Wild" Enterovirus Infections* Coincident with Administration of "Sabin Vaccine"*

Family Status	Age, Yr.	Natural Immunity Status†	Presence of Virus in Feces on Day							
Unit 10: Upper Economic, Index Fed 5.3 Log Dose Type 1			0	1	2	4	7	9	14	21
Father	...	I	—		—	—	—		—	—
Mother	...	I	—		B5	B5	B5	B5		B5
Children	8	S	B5	B5		B5	B5	B5	B5	
→	5	S	B5	B5	1	1	1	1		1
	2	S	B5		B5	B5		B5	B5	B5
Unit 15: Negro, Index Fed 7.3 Log Dose Type 1			0	2	3	6	12	20	38	55
Father	...	I	—		—	—				
Mother	...	I	—		—	2	—	—	—	
Children	6	S	2		2	2	—	—	—	
	5	S	—		2	2	2	—	—	
	4	S	2		2	2	2	—	—	
→	2	S	—	1	1	1	1	1	—	2
Unit 46: Caucasian-Lower Economic, Index Fed 7.1 Log Dose Type 3			0	2	4	5	7	8	10	38
Father	...	I	—	—	—	—	—	—	—	
Mother	...	I	—	—	—	3	—	—	—	
Children	18	I	—	—	—	—	—		—	
	13	I	—	—	—		—	—	—	
	12	S	—	—	—		3		—	3
	10	S	—		E1+3		—	3	—	3
	8	S	E1	E1	E1	3	E1	3	—	3
	5	S	—		E1	—	—	E1	3	3
→	4	S	—	3	3	3	3	3		3
	1	S	E1	E1	E1	—	E1		3	3

* Natural "wild" Enteroviruses: Coxsackie B5, ECHO 1, and poliovirus type 2. Fed "index" child indicated by arrow.
† With reference to vaccine virus type fed. I=immune; S=susceptible.

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V.

does not suggest that the previous sensitization with Salk vaccine had produced an accelerated response, although comparable studies in unvaccinated persons were not done.

Among the 46 family units in which spread of virus from a vaccine-induced infection was studied, the more readily identifiable variables were virus type, virus dose, and the related pharyngeal excretion of virus, socioeconomic status, and age of the index person. Perhaps of at least equal importance in influencing viral transmission are concurrent infections with other enteric viruses and subtle variations in the interpersonal relationships of the individuals comprising these families. Because of the multiplicity of variables and the small numbers of units per identified variable, conclusions as to the influence of individual factors in predisposing to or limiting transmission seem justified only if the results are definite and consistent.

Among the three virus types, there is a suggestion that type 3 ordinarily may spread more readily than either of the others; however, in individual instances, both types 1 and 2 viruses infected all of the contacts. A direct effect of virus dose was not noted, but the larger (7 log) doses resulted in a greater proportion of index pharyngeal excretors, who in turn were associated with more extensive transmission of types 2 and 3. However, the significance of this is weakened by the fact that development of infection of some contacts appeared well after pharyngeal excretion had ceased. Since fecal extracts have not yet been titrated, some association between virus titer in the feces and viral multiplication in the throat cannot be ruled out. Moreover, a possible effect of the larger dose on suppressing or aborting coincidental "wild" virus infections has not been evaluated. Nonetheless, although pharyngeal excretion may have some effect in increasing the probability of virus transmission, the demonstration that spread occurs readily in its absence is of much greater import. This relates to the suggestion by Salk [12] that, if formalinized vaccine reduces pharyngeal multiplication, and if the transmission of poliovirus is by way of pharyngeal excretions in a well-sanitated population, then the widespread use of a formalinized vaccine may reduce the volume of transmission in such a community. Spread certainly did occur in many of these Salk-vaccinated families in the demonstrated absence of pharyngeal excretion of virus. Furthermore, spread of infection did not occur among several families from the upper economic group in which the index person was a mother who was excreting virus from the throat.

The one variable which definitely played a role in controlling the extent of intrafamilial transmission was socioeconomic status. Only 9% of susceptible contacts from the upper economic group became infected as contrasted with 53% among households from the lower economic group. This is a much greater difference than was seen in episodes of natural poliovirus transmission where the infection of almost all susceptible contacts is the rule, regardless of sanitary status. This probably is to be explained by the lesser infectivity of the attenuated strains.

The demonstration of transmission of vaccine viruses outside the family unit to play contacts suggests the possibility that an entire community might be saturated with these strains, if they were administered to a sufficiently large proportion of the susceptible children present. Despite their lower infectivity, the multiple opportunities for contact then available might enable them to compete effectively with other, "wild" strains present in the population, eventually, perhaps, to displace them.

Interference between enteroviruses has been demonstrated often in the laboratory, and has been postulated as an explanation for some peculiarities in the occurrence of epidemics of poliomyelitis and pleurodynia.[13] If this is a phenomenon which occurs under natural conditions, we might expect that the introduction of a related enteric virus into a household coincidentally with the administration of an attenuated strain might inhibit the spread of the latter, as is strongly suggested in certain of our unit studies. Thus, while, in practice, extensive community spread of vaccine polioviruses may be limited in good environments by superior hygienic standards, it may, rather paradoxically, be limited by viral interference in poor environments. If such interference takes place commonly, it might be of great importance in limiting the effectiveness of mass live-virus immunization programs in poorly sanitated areas.

Finally, the total absence during this study of harmful effects consequent to infection with these living, attenuated poliovirus strains is to be noted. Although the persons taking part were few in number, these results may be added to the rapidly growing record of safety which is being accumulated for this method of immunization against poliomyelitis.[8]

Summary

A study of the spread of infection with Sabin's living, attenuated strains of polioviruses was conducted in 56 "Salk-vaccinated" household units in New Orleans. Each unit contained at least three naturally susceptible members, one of whom was fed the oral vaccine. The course of infection in this index person was followed by virologic and serologic means, and spread to other persons within and without the families was similarly studied. The effect of such variables as virus type, virus dose and the related excretion of virus in the pharynx, socioeconomic status, and age of the vaccine recipient was investigated. All except one adult became infected after the feeding of at least 100,000 infectious units, and transmission to many contacts was detected. Socioeconomic status appeared to have the most marked effect on spread, upper status usually

being associated with failure of transmission. Interference to spread of the attenuated strains by other, "wild" enteric virus infections among families from the lower economic group was strongly suggested. No illness was associated with either primary vaccine administration or contact infection.

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HUMAN PHARMACOLOGY OF THIAZIDE DERIVATIVES

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Chlorothiazide in doses of 1 Gm. by mouth twice daily induced the excretion of practically the same amounts of sodium and chloride as did 2 cc. of a molar solution of meralluride injected intravenously. When the chlorothiazide was administered daily for two or three weeks, the sodium excretion declined until it approached the daily intake, and the patient's body weight approached a steady level about 4 lb. (1.8 kg.) below the initial level. A nearly maximal rate of sodium excretion was obtained with 2 Gm. of either chlorothiazide or flumethiazide, and increasing the doses to 4 Gm. did not yield further significant increases of sodium excretion. For hydrochlorothiazide the dose required to give maximum excretion rates was 200 mg. A steadier effect and over-all increase in response resulted from giving doses of 200 mg. of hydrochlorothiazide every 12 hours as compared to 400 mg. given once a day.

Numerous clinical conditions of diverse etiology are associated with sodium and water retention, due usually to increased reabsorption by the renal tubules. Because of the varied causes of edema, a drug, if it is to be effective, must be adequately potent to depress the reabsorption of sodium and water irrespective of the etiology of the retention.

Chlorothiazide (Diuril) is an effective natruretic and diuretic agent when administered orally, and it compares favorably with the organomercurials which are given parenterally. As in the case of the organomercurials, the increase in water excretion is secondary to the natruresis. Although the incidence of serious side-effects after the administration of chlorothiazide is low, a number of derivatives of chlorothiazide have been developed in an effort to find more potent compounds with fewer side-effects. This report presents certain pharmacological properties of chlorothiazide and two of its derivatives,

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flumethiazide (Ademol) and hydrochlorothiazide (Hydrodiuril), placing particular emphasis on the response in electrolyte excretion.

Effect on Electrolyte Excretion

Chlorothiazide inhibits carbonic anhydrase in vitro, being more active than sulfanilamide but less active than acetazolamide (Diamox).[1] In vitro, chlorothiazide exerts its effect primarily in the renal tubules. Some investigators [2] propose that chlorothiazide produces its diuretic response by inhibition of sodium and chloride reabsorption, with subsequent exchange of some of the sodium for potassium in a more distal portion of the tubule, resulting in a moderate increase in potassium excretion. These authors also compared chlorothiazide and meralluride (Mercuhydrin). They concluded that chlorothiazide acts more distally in the renal tubule than meralluride. Presumably flumethiazide and hydrochlorothiazide have the same action.

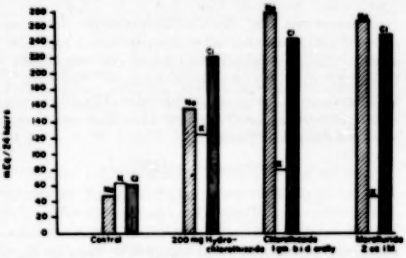

Fig. 1.—Effect on sodium, potassium, and chloride excretion of hydrochlorothiazide as compared to chlorothiazide and meralluride.

Chlorothiazide and the two derivatives (hydrochlorothiazide and flumethiazide) produce effects within 2 hours after oral dosage that reach a maximum within 6 hours; the response persists for 12 hours or more. The primary effect of chlorothiazide is an increase in sodium excretion, with a slightly lesser effect on chloride excretion (fig. 1). There is a moderate and consistent increase in potassium excretion. As a compensatory renal mechanism to conserve sodium, ammonia excretion is increased during the second 12-hour period but shows no increase before that. The increase in the rate of excretion of bicarbonate is about one-fourth that of chloride. Phosphate excretion is not altered. By contrast, a carbonic anhydrase inhibitor such as acetazolamide produces an immediate augmentation of sodium excretion, with an almost equal effect on potassium and bicarbonate excretion. Acetazolamide suppresses chloride excretion during the period of greatest bicarbonate loss, but the former increases when the latter subsides. Phosphate excretion is not affected by carbonic anhydrase inhibitors.

In general, the spectrum of activity of chlorothiazide appears to resemble that of the mercurial agents. As with administration of the thiazide derivatives, the administration of meralluride parenterally is followed by an onset of action within one hour which reaches its maximum in 2 to 6 hours, and the natruretic effect lasts for 12 to 18 hours. An increased excretion of sodium and chloride is the predominant effect,[3] while potassium excretion is not significantly altered (fig. 1). Ammonia excretion, slightly depressed at first, becomes elevated after the period of greatest sodium loss. During the stage of greatest chloride loss, bicarbonate excretion is suppressed, but this returns to normal or higher when the chloruretic response subsides.

The predominant effect of chlorothiazide and flumethiazide is to increase sodium excretion, with a lesser but nearly equal effect on chloride excretion. By contrast, the predominant effect of hydrochlorothiazide is to increase chloride excretion, with a lesser effect on sodium (fig. 1).

Ford [4] compared the response to chlorothiazide given alone and in combination with meralluride or the carbonic anhydrase inhibitor acetazolamide. With the former combination, the response was additive. With the latter combination, the maximum chloride output was only one-half that of sodium and the bicarbonate loss was fourfold to sixfold greater than that which occurred when chlorothiazide alone was given.[4] There was a modest increase in sodium excretion. It appears from both preclinical and clinical studies that the effects of chlorothiazide on sodium excretion are additive to those of mercurial diuretics as well as to the response to carbonic anhydrase inhibitors. It is quite possible that chlorothiazide shares a common mechanism of action with meralluride and another with acetazolamide but that it also acts through a third, noncompetitive mechanism.[5]

Both meralluride and the thiazide derivatives reverse the effects of vasopressin (Pitressin), which normally decreases urine flow but does not alter the rate of electrolyte excretion. When chlorothiazide or meralluride is given to dogs who have previously received vasopressin, the urine flow is increased and sodium, potassium, and chloride excretion rates are greatly increased also. The urine is hypertonic with respect to both sodium and chloride, suggesting that the effect is at least partly attributable to a direct influence of chlorothiazide on renal tubular electrolyte transport.

Chlorothiazide also reverses the inhibitory effect of various steroids on salt excretion. When cortisone, hydrocortisone, or fludrocortisone is given to adrenalectomized dogs, sodium excretion is suppressed and potassium excretion is augmented; consequently, the sodium-potassium ratio declines. When chlorothiazide is given at this stage, the sodium excretion increases considerably, with an accompanying small increase in potassium excretion. The relatively greater increase in sodium out-

put tends to raise the sodium-potassium ratio toward normal. Similar observations have been made on patients who were receiving steroids therapeutically.

With continuous daily administration, chlorothiazide has repetitive action (fig. 2). Increased sodium excretion continues until body stores of sodium have been reduced (fig. 2). Serum concentrations of chloride and potassium are slightly depressed, while that of bicarbonate is slightly elevated. The natruretic effect of mercurials is qualitatively similar to that of chlorothiazide. The trend toward hypochloremic alkalosis is sometimes observed with the administration of thiazide derivatives, especially hydrochlorothiazide.

Observations on Renal Hemodynamics

Doses of 0.5 mg. and 10 mg. of chlorothiazide per kilogram of body weight given intravenously appeared not to have a significant effect on mean blood pressure. Glomerular filtration rate was not affected by the 0.5-mg. dose, but after the 10-mg. dose it was slightly depressed, probably as a response to the water and sodium loss (dehydration phenomenon) associated with the diuresis.[3a] It is not likely that chlorothiazide inhibits the renal tubular extraction of para-aminohippurate, since para-aminohippurate clearance was not reduced at the time that chlorothiazide exhibited its maximum effect. In conclusion, the diuretic response to chlorothiazide cannot be attributed to an increase in glomerular filtration rate, indicating that the diuretic response results from blockade of water and electrolyte reabsorption in the renal tubules.

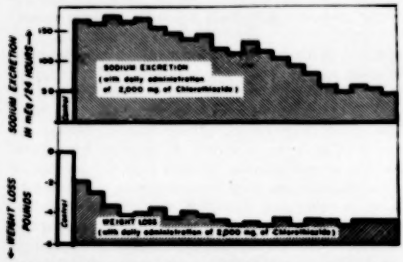
SODIUM EXCRETION in mEq/24 HOURS
SODIUM EXCRETION (with daily administration of 2,000 mg. of Chlorothiazide)
Control
WEIGHT LOSS in POUNDS
WEIGHT LOSS (with daily administration of 2,000 mg. of Chlorothiazide)

Fig. 2.—Effect of continuous administration of chlorothiazide on sodium excretion and weight loss in patient with minimal edema. After two to three weeks' daily therapy, sodium excretion approximates intake. This occurs as the body stores become depleted. Despite this approximation, weight loss is maintained.

Similar observations have been made on flumethiazide. When 800 mg. of flumethiazide was given orally to patients in heart failure, there was a sharp increase in sodium excretion one hour after the drug was given (fig. 3), and this persisted throughout the period of observation (five hours). There was no effect on mean blood pressure, glomerular filtration rate (fig. 4), or renal plasma flow. Despite the marked natruresis, plasma sodium and potassium concentrations were not altered.

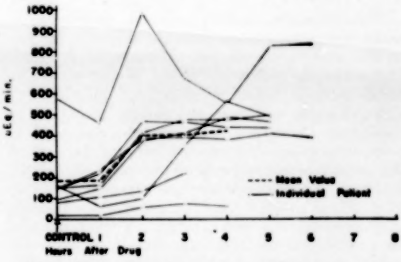

Fig. 3.—Effect of flumethiazide on sodium excretion after single dose of 800 mg. given orally.

Observations on hydrochlorothiazide likewise showed no significant alteration in renal hemodynamics after the administration of 100 mg. orally. When 200 mg. was given intravenously, there was a temporary reduction in glomerular filtration rate which returned to control levels within one hour after the drug was given.

Bioassay Studies

Dose response curves, with sodium excretion used as the critical modality, were determined for patients who were on a controlled sodium intake. Since the patients were in electrolyte balance on a diet containing 50 mEq. of sodium, the control excretion in the urine was approximately 90% of the dietary sodium (about 45 mEq.). The average increase in the 24-hour urinary sodium excretion after chlorothiazide was 44 mEq. after the 500-mg.

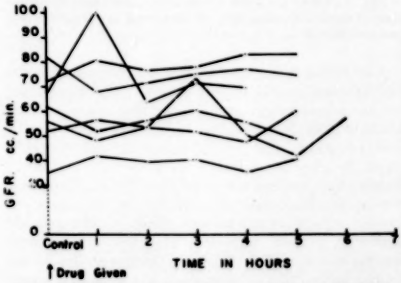

Fig. 4.—Effect of single 800-mg. oral dose of flumethiazide on glomerular filtration rate. Lines indicate responses of individual patients. There was no evidence of significant increase or reduction in glomerular filtration rate within six hours after administration.

dose and 104 mEq. after the 2,000-mg. dose (fig. 5). There was no additional natruresis when the dose was increased above 4 Gm. and very little increase when the dose was increased from 2 to 4 Gm. (fig. 5). Similar observations were made when flumethiazide was administered (fig. 6). The curve

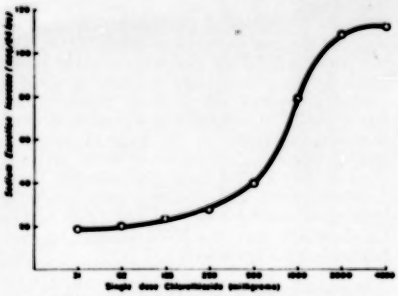

Fig. 5.—Curve of response to chlorothiazide, with increase in sodium excretion used as reference point. Minimal effective dose appeared to be between 125 and 250 mg. Dose which produced maximum increase in excretion was about 2,000 mg. Increase was not significant when dose was increased from 2,000 to 4,000 mg. (Reproduced from Ford and others: *A. M. A. Arch. Int. Med.* 100:582 [Oct.] 1957.)

of response to hydrochlorothiazide is shifted to the left. A significant increase in sodium excretion starts at the 25-mg. dose and increases to a maximum at the 200-mg. dose level (fig. 7). This appears to be the maximum effective dose level, and no further increase in sodium excretion is produced by a dose larger than 200 mg. The chloruretic response was noticeably larger than the natruretic response, and potassium excretion was approximately one-half that of sodium. At maximum responses for chlorothiazide and hydrochlorothiazide, the increase in sodium excretion was the same, although the dose required to produce this maximum effect with hydrochlorothiazide was only about 10% of that required with chlorothiazide.

When potency of chlorothiazide is compared with that of other diuretics, it appears that a dose of meralluride (1 cc.) equivalent to 40 mg. of mercury produces an increase in sodium excretion that is equivalent to about 1,000 mg. of chlorothiazide administered orally, and 700 mg. of chlorothiazide is equivalent to 1 cc. of mercaptomerin (Thiomerin) administered parenterally. When both drugs are administered orally, four tablets (equivalent to 40 mg. of mercury) of chlormerodrin (Neohydrin) are equivalent in natruretic potency to 560 mg. of chlorothiazide. The response to flumethiazide is about the same at equal doses. The response to hydrochlorothiazide is also about the same, but at 10% of the dose of chlorothiazide.

To determine differences in sodium and potassium excretion for chlorothiazide given as a single dose and as fractional doses per 24 hours, the sodium and potassium excretion was observed in a patient who received 4,000 mg. as a single dose at 6 a. m. After a suitable recovery period (seven days) the drug was given as 1,000 mg. every six hours for four doses. There was a greater potassium loss on the fractional dose schedule. However, there was an even greater sodium loss, indicating the advantage of fractional doses. Similar observations have been made with flumethiazide and hydrochlorothiazide (fig. 8).

Nervous System Effects

Chlorothiazide appears to be free of actions on the nervous system. Consequently, it does not have appreciable antiepileptic, anesthetic, analgesic, or antiglaucomatous effects. Unlike acetazolamide, it apparently does not penetrate the blood-brain barrier and is consequently not distributed through the

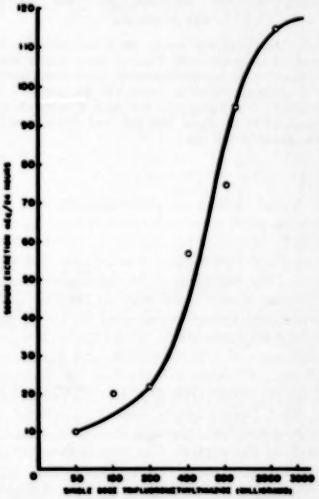

Fig. 6.—Curve of response to flumethiazide (trifluoromethylthiazide). Curve is similar to that observed after administration of chlorothiazide (fig. 5).

central nervous system in appreciable concentration. For this reason it produces little effect referrable to the central nervous system.

Evidence indicates that chlorothiazide, even in large intravenous doses, has no significant effect on the cardiovascular-respiratory system of anesthetized dogs. Cardiovascular effects of injected acetylcholine, histamine, epinephrine, and nicotine were

unaltered by chlorothiazide, as was the reflex pressor effect of central vagal stimulation. No effect was noted on mean arterial blood pressure or heart rate. These findings indicate that the drug does not possess significant antihistaminic, adrenergic-blocking, atropine-like, or ganglionic-blocking activity.

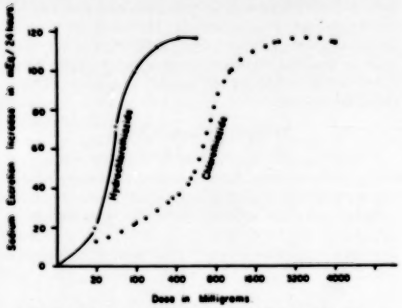

Fig. 7.—Dose-response curve for hydrochlorothiazide as compared to chlorothiazide. Curves were similar but with smaller dose of hydrochlorothiazide. However, greater increase in sodium excretion could not be obtained by its administration. Maximum effective dose of hydrochlorothiazide appeared to be about 200 mg. and that of chlorothiazide was about 2,000 mg.

Clinical Use

The initial dosage of chlorothiazide and flumethiazide in edematous subjects is 1 to 2 Gm. daily, and for hydrochlorothiazide it is 100 to 200 mg. daily for three to five days or until overt edema disappears. This is followed by administration of a maintenance dose of 250 mg. to 1.0 Gm. of chlorothiazide and flumethiazide and 25 to 100 mg. of hydrochlorothiazide daily. Total daily amounts of over 500 mg. of chlorothiazide and flumethiazide and 50 mg. of hydrochlorothiazide are customarily given in two divided doses at 8-to-12-hour intervals. Since these compounds exhibit a rising dose-response curve,[39] the dosage should be adjusted to the needs of the patient. Therapy in severely ill patients is started at higher dosage levels than in those with moderate or mild edema. The dosage and frequency of administration should be readjusted subsequently according to the patient's response.

In mild or moderate edema, smaller doses and intermittent administration, for two or three days per week, may be preferable. Occasionally even severely ill patients will respond better to intermittent administration (three days per week).

For premenstrual tension, therapy with 500 mg. of chlorothiazide or flumethiazide or 50 mg. of hydrochlorothiazide daily is usually started five to seven days before the period and discontinued at the onset of menses. In edema of pregnancy, with or without hypertensive vascular disease, similar daily doses for five days per week are recommended. Lower doses have failed to produce sufficient initial diuresis.

When the thiazide derivatives are first administered to hypertensive patients being treated with other drugs, it is advisable to continue giving Rauwolfia derivatives in the standard dosage and to reduce the dose of the other agents (fig. 9). The dose particularly of the ganglionic-blocking agents should be reduced one-half or more (to avoid a possible precipitous fall in blood pressure), and then it should be increased or decreased in small increments according to the patient's response. Careful, repeated observations of blood pressure, especially during initial therapy, are essential. Doses of chlorothiazide and of other antihypertensive drugs given simultaneously can sometimes be further decreased, once the blood pressure becomes stabilized at the lower level.

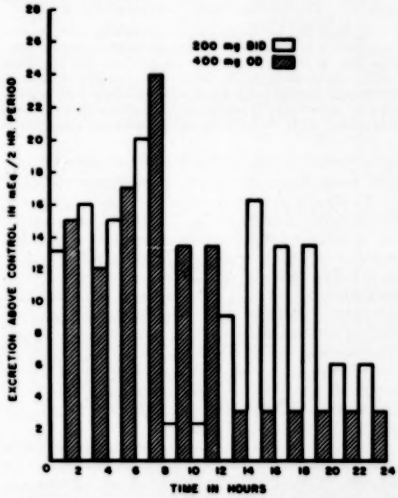

Fig. 8.—Natruretic response to hydrochlorothiazide, 200 mg. every 12 hours as compared to 400 mg. given once a day. Although there was somewhat larger response initially to 400-mg. dose, significant increase in excretion occurred when second 200 mg. was given in twice-a-day regimen.

Therapeutic Precautions

Edema syndromes, particularly heart failure, may be associated with electrolyte abnormalities. Some of these are due to coexistent gastrointestinal, hepatic, renal, or pulmonary disturbances, while others may be the result of intensive or excessive use of therapeutic agents. These electrolyte dis-

turbances may cause serious symptoms and may also render the underlying disease unresponsive to therapeutic regimens. An electrolyte imbalance should be suspected (and confirmed by chemical studies) in all patients whose conditions become refractory to diuretic agents. However, when careful appraisal shows that both symptoms and electrolyte disturbances arise from progression of the underlying disease, diuretic therapy will probably be of no avail. Electrolyte disturbances caused by vigorous diuretic therapy, on the other hand, can usually be readily corrected.

Hypochloremic alkalosis may be avoided by a judicious adjustment of the dosage and frequency of administration of thiazide derivatives and by avoidance of rigid salt restriction. This side-effect is most likely to occur in association with the administration of hydrochlorothiazide, since the primary effect of this agent is to increase chloride excretion rather than sodium excretion. This response is in contrast to that with the other thiazide derivatives. Temporary cessation of drug therapy or the administration of ammonium chloride prevents or corrects the alkalosis if it does occur. The therapist should remember that, in patients with hepatic insufficiency, ammonium salts can produce ammonium intoxication. The low-salt syndrome as a complication of therapy with the thiazide compounds does occur occasionally. When the history and blood electrolyte studies establish the fact that sodium depletion is present, salt can be given by mouth or a cautious infusion of hypertonic sodium chloride may be used. Water should rigidly be restricted while the infusion is being given and for three to six hours thereafter. Diuretic therapy is usually discontinued until the reestablishment of a normal or nearly normal blood electrolyte pattern.

Intensive or prolonged administration of chlorothiazide and its derivatives may produce hypokalemia. Mild depression of serum potassium level usually produces no symptoms. As the potassium deficit accumulates, gradual diminution of strength is noted; the muscles tend to become flaccid and the reflexes, hypoactive or absent. The patient may complain of weakness only, or of numbness of the extremities. When the hypokalemia is severe, symptoms include apathy, drowsiness, anorexia, nausea, paralytic ileus, hypotension, and shallow, infrequent respiration. Hydrochlorothiazide is more likely to produce potassium depletion (hypokalemia) than are chlorothiazide and flumethiazide.

Significant electrocardiographic changes may appear when the serum potassium level drops to 3 mEq. per liter or lower. These are prolongation of Q-T interval due mainly to flattening and widening of the T wave, T-wave inversion, and depression (sagging) and low "take-off" of the S-T segment. These changes may occur independently or in combination.

Hypopotassemia sensitizes the myocardium to the action of digitalis and may result in digitalis toxicity. This is indicated by cardiac arrhythmias, most often paroxysmal auricular tachycardia with block. Treatment consists of omitting digitalis and administering potassium, preferably orally, care being taken not to bring on potassium intoxication.

Prophylactic administration of potassium chloride or citrate (1 to 6 Gm. daily) along with chlorothiazide is particularly recommended in patients with conditions which may be associated with potassium deficiency, especially with fever or when excessive loss (with diarrhea) is imminent. Potassium deficiency may also develop during the administration of some adrenocortical steroids.

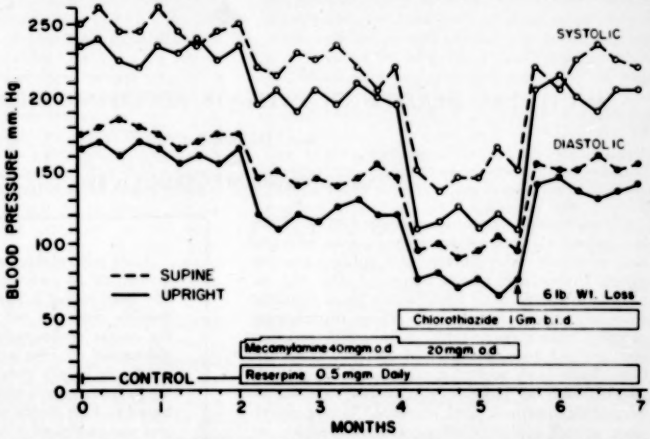

Fig. 9.—Effect of chlorothiazide on blood pressure response to rauwolfia and ganglionic-blocking agent in hypertensive patient with left ventricular strain. Even with one-half the original dose of blocking agent, reduction in blood pressure was much greater than that observed while patient was taking rauwolfia and mecamylamine without diuretic. (Reproduced with permission from *Ann. New York Acad. Sc.* 71:436, 1958.)

Conclusions

In the final analysis, diuretic therapy is only one important facet of the management of edematous patients. An effort must always be made to correct the underlying abnormality when specific therapy is available.

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ACUTE PANCREATITIS IN PATIENTS RECEIVING CHLOROTHIAZIDE

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Acute pancreatitis was diagnosed in three women, all 50 years of age or older, who had been taking 0.5 to 1.0 Gm. of chlorothiazide daily for two or three months in the course of treatment for cardiovascular disease. In no case was there a history of conditions usually considered as predisposing to acute pancreatitis. The diagnosis was based on both clinical and laboratory studies and was confirmed in one case by histological study of autopsy material. Although the specific etiology remained undetermined, chlorothiazide was considered as a possible cause. The authors wish to alert physicians to this possibility, which may warrant further investigation.

Chlorothiazide, since its introduction in 1958, has gained widespread acceptance as an effective and relatively safe diuretic and antihypertensive agent. Undesirable effects occurring after the use of chlorothiazide have been largely those resulting from electrolyte disturbances. These disturbances actually reflect exaggerated therapeutic responses and are not true reactions of toxicity. However, there have been scattered reports of direct toxic effects, such as papular skin rashes,[1] exfoliative dermatitis,[2] purpura,[3] and jaundice.[4] In our experience, as well as that of others, such toxic effects are extremely rare; however, within the past year we have observed the development of severe acute pancreatitis in three patients who had been taking chlorothiazide daily for several months. These patients did not have any of the usual precipitating causes of acute pancreatitis, such as associated cholecystic disease, pancreatic tumor or infection, injury to the pancreas, or alcoholism. It seems timely, therefore, to call to the attention of others the possibility that pancreatitis may be a complication of chlorothiazide therapy. A report of these three cases follows.

Report of Cases

Case 1.—The patient was a 78-year-old widow who had severe arteriosclerotic heart disease. Control of her symptoms of congestive heart failure had required salt restriction, digitalis therapy, and injections of meralluride three times per week. On Jan. 7, 1958, the meralluride therapy was discontinued and the administration of 1 Gm. of chlorothiazide daily was begun. The digitalis therapy was continued, but no other medicaments were given. Satisfactory control of the congestive heart failure ensued and the patient noted that taking the chlorothiazide daily freed her from the "ups and downs" of intermittent mercurial diuresis.

From the Division of Medicine, Lexington Clinic.

At 4 a. m. on April 1, 1958, she was awakened by severe abdominal pain and repeated vomiting. She was seen shortly thereafter at home. Physical examination revealed an acutely ill, cyanotic, elderly female in severe distress. The skin was cold and moist. The cardiac sounds were of fair quality, the rate was 72 beats per minute, and the rhythm was completely irregular. The lungs were free of rales. The abdomen was distended and silent; tenderness was present in the epigastrium and right upper quadrant. Results of rectal and pelvic examinations were negative. The peripheral pulsations were intact.

The patient was admitted to the hospital later that morning. Laboratory studies done about seven hours after the onset of her pain revealed an erythrocyte count of 4,930,000 and leukocyte count of 21,000 per cubic millimeter of blood, with 87% neutrophils, of which 11% were band forms. The concentration of hemoglobin was 14.2 Gm. per 100 cc. of blood. Results of urinalysis were negative. The serum amylase level was 1,630 units per 100 cc. A plain roentgenogram of the abdomen revealed a few gas-containing loops of small intestine but no free air or abnormal calcifications.

The diagnosis of pancreatitis was obvious, and the patient was treated with sedation, administration of atropine, nasogastric suction, and fluid replacement. On the third hospital day the serum amylase level was 562 units per 100 cc. However, the patient's condition steadily worsened, and 75 hours after the onset of abdominal pain she died. Postmortem examination revealed severe hemorrhagic pancreatitis with widespread fat necrosis. The liver, gallbladder, and bile ducts were normal.

Case 2.—The patient was a 52-year-old married female who had had moderately severe hypertensive vascular disease for several years. Two years previously she had had an acute cerebrovascular accident resulting in a spastic right-sided hemiparesis. Her blood pressure had ranged from 190 to 250 mm. Hg systolic and from 118 to 120 mm. Hg diastolic. On July 14, 1958, her blood pressure was 210 mm. Hg systolic and 130 mm. Hg diastolic. At that time the administration of 5 mg. of mecamylamine and 500 mg. of chlorothiazide daily was begun.

On Nov. 6, 1958, the patient was admitted to the hospital because of severe abdominal pain, nausea, vomiting, weakness, and polyuria. Physical examination revealed a confused, drowsy, dehydrated, obese woman. Her blood pressure was 190 mm. Hg systolic and 115 mm. Hg diastolic. The cardiac rate was regular and the heart was of normal size, but there was a grade 1 systolic apical murmur. Examination of the ocular fundi revealed grade 2 hypertensive changes. Dental caries and marked periodontoclasia (pyorrhea alveolaris) were present. The abdomen was distended, tender, and silent. The concentration of hemoglobin was 16.6 Gm. per 100 cc. of blood. The erythrocyte count was 6,100,000 and the leukocyte count 10,800 per cubic millimeter of blood, with 87% segmented neutrophils, 5% band neutrophils, 7% lymphocytes, and 1% monocytes. The sedimentation rate was 49 mm. in one hour (Westergren method). Urinalysis revealed a specific gravity of 1.028, glycosuria (4+) and acetonuria (2+). Results of microscopic examination of the urine were negative. The blood glucose level was 1,200 mg.%. The serum amylase level was 700 units per 100 cc. (corrected for the high glucose level in the blood). The cerebrospinal fluid was normal. The blood urea nitrogen level was 100.8 mg.%.

On the second hospital day the patient developed shock, her temperature rose to 104 F (40 C), and she became comatose. A constant intravenous infusion of arterenol was required to sustain her blood pressure level. However, with the help of intravenous administration of fluids, maintenance of constant gastric suction, and administration of anticholinergic drugs and insulin, she slowly regained consciousness, her abdominal pain disappeared, and her blood urea nitrogen and fasting blood sugar returned to normal levels. The serum amylase level was 280 units per 100 cc. on the 5th hospital day, 365 units on the 8th day, and 50 units on the 12th day. Roentgenograms of the gallbladder and upper part of the gastrointestinal tract taken when the patient became ambulatory were normal. An electrocardiogram revealed a pattern of left ventricular hypertrophy. On the 48th hospital day the patient was transferred to a nursing home for continued supportive care.

She was seen again on Jan. 12, 1959, in the outpatient department of the hospital. Her blood pressure was 200 mm. Hg systolic and 130 mm. Hg diastolic. She felt well and had had no further abdominal pain. Urinalysis revealed no sugar or acetone. The fasting blood sugar level was normal, and the administration of insulin was no longer necessary.

Case 3.—The patient was a 71-year-old widow who had been chronically ill with rheumatic heart disease, mitral insufficiency, and chronic congestive heart failure for about three years. She had been on a low-salt diet and therapy with digitoxin and mercurial diuretics until December, 1958, when the administration of chlorothiazide, 0.5 Gm. daily, was substituted for the mercurial diuretics.

On March 30, 1959, the patient suddenly began to have severe generalized abdominal pain with nausea and vomiting. The pain was steady and only temporarily relieved by administration of meperidine hydrochloride. The patient was, therefore, admitted to the hospital. She had no family history of pancreatitis. She never had consumed alcoholic beverages. Physical examination revealed an acutely ill, nauseated, dyspneic female. The blood pressure was 170 mm. Hg systolic and 100 mm. Hg diastolic. The pulse rate was 80 beats per minute. The respira-

tions were rapid and shallow. Her temperature was 97 F (36.1 C). Examination of the ocular fundi revealed arteriolar sclerosis, grade 2 (according to the classification of Keith, Wagener, and Barker). The heart was enlarged to the left anterior axillary line, with a diffuse, heaving, apical impulse and a grade 4 systolic apical murmur. Auscultation of the lungs revealed a few medium moist rales in both bases. Abdominal examination revealed generalized tenderness, which was most marked in the upper part of the abdomen, accompanied by involuntary muscle spasm and rebound pain. There was moderate gaseous distention, and peristaltic activity was markedly decreased. The peripheral pulses were full and equal, and there was no pitting edema of the ankles or legs. Results of rectal examination were negative. The patient was somewhat confused and irrational. Her lips were cyanotic. The concentration of hemoglobin was 11.9 Gm. per 100 cc. of blood. The leukocyte count was 16,150 per cubic millimeter of blood, with 94% segmented neutrophils. Urinalysis revealed albuminuria (1+) and 2 to 3 white blood cells per high-power field. The serum amylase level was 925 units per 100 cc. A plain roentgenogram of the abdomen revealed a calcified, tortuous aorta but no other abnormality. The roentgenogram of the chest revealed the lung fields to be clear but the heart markedly enlarged. The blood calcium level was 7.5 mg.%.

The diagnosis of acute pancreatitis was made. The patient's severe abdominal pain persisted, and she was treated with constant gastric suction and administration of anticholinergic drugs, sedatives, mercurial diuretics, digitoxin (Crystodigin), penicillin, and streptomycin. Because of cyanosis and respiratory distress, administration of oxygen was necessary during the first week of hospitalization. Over a period of nine days the patient's condition slowly improved. Her abdominal pain disappeared, she became mentally clear and rational, the cyanosis disappeared, the dyspnea markedly improved, and she was able to take a soft diet without difficulty. Roentgenograms of the gallbladder and upper part of the gastrointestinal tract on the 14th hospital day were normal. The serum amylase level just prior to the patient's dismissal was 70 units per 100 cc.

Comment

In the majority of cases of acute pancreatitis, either alcoholism or associated disease of the biliary tract is present. In a statistical review, Paxton and Payne [5] found either associated cholecystic disease or alcoholism in 62% of 307 established cases of acute pancreatitis. In the remaining 38% of the cases the etiology of the disease was unknown. To our knowledge, no drug or chemical other than alcohol has been incriminated as an etiological factor in pancreatitis. However, our observation during the past year of the development of severe acute pancreatitis in three patients who were receiving chlorothiazide leads us to suspect that this may be more than a coincidence. None of these three patients was an alcoholic or had associated biliary tract disease. All were middle-aged or elderly females. All had received chlorothiazide daily for several months. None had developed any untoward digestive symptoms or evidence of gastric irritation. None had a family history of pancreatitis. All had serious vascular disease. The pancreatitis was fatal in one case. The other two patients recovered, after prolonged hospitalization.

Summary and Conclusions

During the past year we have observed the development of acute pancreatitis in three patients (all middle-aged or elderly females) who had been receiving chlorothiazide daily for several months and who did not have associated biliary tract disease, alcoholism, or any other of the conditions usually considered important in the etiology of pancreatitis. By reporting these cases, we hope to draw the attention of others to the possible development of pancreatitis in patients who receive chlorothiazide.

Addendum

Since the submission of this manuscript, we have observed a fourth example of pancreatitis associated with the administration of chlorothiazide. The patient is an 84-year-old man with arteriosclerotic heart disease and chronic congestive heart failure, who had taken 1 Gm. of chlorothiazide once or twice a week for 15 months. He is now in the hospital with typical acute pancreatitis. The initial serum amylase level was 890 units per 100 cc. To date he is not well enough for cholecystography, but he gives no history suggestive of gallbladder disease. He has never used alcoholic beverages.

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CLINICAL THERAPEUTIC EVALUATION OF HYDROCHLOROTHIAZIDE (HYDRODIURIL)

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and
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In most patients treated earlier with chlorothiazide, maintenance of the previous status was obtained with a dose of hydrochlorothiazide one-tenth that of chlorothiazide. An important advantage appears to be absence of complaints of weakness during early weeks of treatment. Intravenous administration of hydrochlorothiazide is convenient and effective therapy. In oral therapy, daily administration is preferred because a more constant level of "compensation" is desirable. Hypertensive patients without clinical congestive failure showed improvement both symptomatically and by fall in blood pressure.

The advent of chlorothiazide initiated a new era in diuretic therapy. Since its evaluation by an unusually large number of investigators, this remarkable compound has become a valuable therapeutic tool for countless practicing physicians. Orally given chlorothiazide is as powerful a diuretic as parenterally given mercury and does not itself become ineffective with continued use.[1] It resembles structurally the carbonic anhydrase inhibitors and pharmacodynamically the organomercurial diuretic drugs. The primary effect appears to be inhibition of renal tubular reabsorption of sodium and chloride, resulting in a secondary increase in water excretion. There appears to be some carbonic anhydrase inhibitory effect on the renal tubules, particularly with the use of larger doses.[2]

Further exploration of the benzothiadiazine chemistry by Novello and Sprague resulted in the synthesis of hydrochlorothiazide (Hydrodiuril), the dihydro derivative of chlorothiazide, having no double bond in the heterocyclic ring. Renal clearance studies show that hydrochlorothiazide is cleared by the kidney at a rate greatly in excess of glomerular filtration, attributable to secretion by the epithelial cells of the renal tubule. Preclinical evaluation with various doses demonstrated that the increase in cation excretion that resulted from increasing the dose of hydrochlorothiazide was completely covered by an equal increase in chloride excretion. In the case of chlorothiazide, however, a portion of the cation was covered by an increased bicarbonate excretion (increase in urine pH). The kaliuretic effect in these experiments was the same for both compounds. These findings may be of significance in assessing the clinical results with these compounds.

Materials and Methods

Case Material.—One hundred eighteen patients were selected for treatment with hydrochlorothiazide, of whom 106 were outpatients. Duration of therapy was approximately four months (18 weeks for 69 patients and 17 weeks for 37 patients). Studies with chlorothiazide had been done previously in the majority of these patients; they were classed with those having edema of marked severity, since poor response to organomercurial therapy was seen prior to the administration of chlorothiazide.[3]

From the Department of Medicine, Cardio-Pulmonary Laboratory, Division I, Kings County Hospital Center.

Group A included 83 patients previously treated with chlorothiazide, of whom 9 had Laennec's cirrhosis, 32 hypertensive heart disease, and 42 arteriosclerotic heart disease. In regard to severity of heart disease, 26 patients were in functional class 4 and 48 in class 3 (New York Heart Association classification). Group B included 35 patients not previously treated with chlorothiazide. Twenty-three patients in this group received hydrochlorothiazide orally and 12 received this agent intravenously (LyoHydrodiuril). Those receiving the drug orally included six patients with hypertension (without clinical evidence of congestive failure), one with Laennec's cirrhosis, seven with hypertensive heart disease, and nine with arteriosclerotic heart disease. Those receiving the drug intravenously included two patients with Laennec's cirrhosis, four with hypertensive heart disease, and six with arteriosclerotic heart disease. There were 5 class 4 and 11 class 3 patients among those with cardiac disease who received the drug orally and 3 class 4 and 7 class 3 patients who received it intravenously.

Poor response to organomercurial therapy was a requirement for those patients in group A prior to their original treatment with chlorothiazide; this requirement was not strictly used in the present study for patients in group B, for the practical reason that patients who show poor response to organomercurials and in whom chlorothiazide has not been tried are difficult to find. It is possible, therefore, that the group B patients may not be

considered as severely ill as were those in group A prior to chlorothiazide therapy; nevertheless, the patients with cardiac failure certainly were among the most edematous of those seen at Kings County Hospital Center.

Thirteen patients with hypertension, who had not previously received chlorothiazide, were given hydrochlorothiazide orally; six of these patients had no clinical evidence of salt and water retention. They are included in this study with the realization that patients with "essential" hypertension may have a slightly elevated serum sodium concentration, expanded total body sodium content, and increased amounts of sodium and water in arterial walls.[4]

Method.—No change in routine was made for the patients in group A (previously treated with chlorothiazide), with the exception of simply substituting hydrochlorothiazide for chlorothiazide. In group B, all diuretic therapy was discontinued, and hydrochlorothiazide was added to the therapeutic regimen. Other than these changes, all measures remained the same and no withdrawal period was used. The patients in this study seldom have been given a low-sodium diet, and they were asked to continue their previous habits—little urging was required. Patients were examined at weekly intervals, and appropriate laboratory studies were done as indicated.

Dosage.—Hydrochlorothiazide was supplied in 25-mg. and 50-mg. compressed tablets and in ampuls containing 50 mg. as powder for reconstitution with distilled water for intravenous use. Patients who had previously received chlorothiazide were given hydrochlorothiazide at one-tenth the dose of chlorothiazide. In group B, those with class 3 cardiac disease were given 50 mg. of hydrochlorothiazide twice daily, as were those with hypertension without overt evidence of congestive failure. Patients with class 4 cardiac disease and those with cirrhosis were given 100 mg. of hydrochlorothiazide twice daily. Patients who received the drug intravenously were given 50 mg. of hydrochlorothiazide in 5 ml. of distilled water once a day; 8 of these 12 patients received two to four such treatments at two-day intervals.

In general, for patients receiving oral therapy, daily administration is preferred in the belief that a more constant level of "compensation" is desirable; this is thought to be one of the main advantages of benzothiadiazine therapy over that with organomercurial agents, which, of necessity, are rarely given daily. To give the benzothiadiazines on an intermittent schedule would eliminate this advantage. From a practical standpoint, the patient is less likely to make mistakes if the habit of administration is a daily one. One dose daily is, of course, ideal if this is sufficient to maintain the desired status; if more than one dose is required, administration at breakfast and at the evening meal is advised, since this approximates 12-hour intervals and eliminates the need for working patients carrying a dose of the drug for midday administration. On this regimen, some patients complain of the necessity of arising at night to urinate, and in these instances administration at breakfast and at lunch is then substituted.

Results

In the majority of the 83 patients previously treated with chlorothiazide, maintenance of the previous status was obtained with a dose of hydrochlorothiazide one-tenth that of chlorothiazide. In approximately one-fourth of these patients, the 10:1 dosage relationship did not hold true, and further adjustment was necessary, with dosage relationships usually resulting in a final ratio of 10:1.5 or 10:2. This minor difficulty offers only temporary inconvenience in changing from chlorothiazide to hydrochlorothiazide therapy. Among the patients who had not previously received chlorothiazide, the original estimated dose requirement was found to be correct for most patients, i. e., 50 mg. of hydrochlorothiazide twice daily for patients with class 3 heart disease and for those with hypertension without overt congestive failure and 100 mg. twice daily for those with class 4 heart disease and for those with cirrhosis. Individual variations were, of course, encountered, and the over-all dosage range is from 25 mg. to 300 mg. daily. One exceptional patient received 450 mg. of hydrochlorothiazide daily and 2 ml. of meralluride three times a week; this patient was formerly receiving 4.5 Gm. of chlorothiazide daily plus the same dose of meralluride. The effective period of action appears to be somewhat shorter for hydrochlorothiazide than for chlorothiazide, and administration three times daily was instituted for approximately one-fifth of patients.

Maintenance of edema-free, compensated status in 83 patients previously treated with chlorothiazide was accomplished with the doses noted above. In 17 patients who had never received chlorothiazide, hydrochlorothiazide produced the same dramatic improvement now familiar with chlorothiazide. Weight and water loss, improvement in the general sense of well-being, diminution or disappearance of edema, and improvement in symptoms were again noted.

No patient in the present study can be classed as showing a therapeutic failure. Only one patient received meralluride; in all other instances control of congestive failure was achieved with digitalis and hydrochlorothiazide, without other adjunctive therapy.

Hypertension.—Patients who had previously received chlorothiazide demonstrated no further change in blood pressure. Patients being treated with antihypertensive agents (usually reserpine) other than chlorothiazide demonstrated a further fall in blood pressure in the order of 20 to 30 mm. Hg systolic and 0-10 mm. Hg diastolic when hydrochlorothiazide was added.

Of six patients with essential hypertension without clinical evidence of congestive heart failure who had never received chlorothiazide and who received no therapy other than hydrochlorothiazide, all demonstrated an improvement in blood pressure and in symptomatology. The range of fall in blood pressure was 50-80 mm. Hg systolic and 10-20 mm. Hg diastolic, usually occurring within the first week of therapy. Postural hypotension was not troublesome symptomatically, though it was occasionally noted on examination. Five of these six patients also had a loss of weight of 3 to 5 lb. (1.3 to 2.3 kg.), which may be considered as water loss. It seems reasonable to suppose that at least a part of the antihypertensive action of hydrochlorothiazide is referrable to improvement of abnormal salt and water metabolism in hypertensive patients presumably free of congestive failure.

Side-effects.—Three patients discontinued hydrochlorothiazide treatment after two to three weeks because of epigastric distress. Two patients developed elevated serum uric acid levels, and one complained of aching knee joints. It has been suggested that these patients have "latent gout" and that the high uric acid levels are due to concentration effects by hydrochlorothiazide in cases of previous decompensation; a more tenable explanation postulates a direct effect on renal tubular metabolism.

No adverse effect on liver function findings or blood cellular constituents was noted. There was no significant change in blood urea nitrogen levels. One patient with Laennec's cirrhosis experienced generalized pruritus and mild diarrhea for two days after the administration of 50 mg. of hydrochlorothiazide intravenously.

Blood Electrolytes.—Changes in serum sodium concentration have been small in degree, inconstantly found, and within normal ranges in all instances. A small drop in serum chloride concentration was common and tended toward reversal by the second week of therapy. There was no significant change in carbon dioxide content.

With chlorothiazide therapy, a significant number of patients complain of weakness during the first one to two weeks of treatment; this symptom disappears usually spontaneously and sometimes with the addition of potassium, either in diet or by tablet. Some instances of proved hypokalemia have been demonstrated. In the present study with hydrochlorothiazide, no evidence of hypokalemia has been demonstrated by serum or electrocardiographic study. No patient was given supplementary potassium chloride or dietary potassium. More significantly, no patient complained of weakness at any time during the study. This finding appears to be the most distinct advantage of hydrochlorothiazide over chlorothiazide.

The lack of weakness with hydrochlorothiazide is certainly a welcome finding, but the explanation remains obscure. Because of the difficulty in proving hypokalemia, it has been supposed that the weakness seen with chlorothiazide therapy was related to low potassium content not demonstrated chemically or electrocardiographically. In a recent series of cases of pregnant women with edema treated with chlorothiazide, approximately two-thirds complained of weakness within the first 48 hours of therapy.[5] It is easy to imagine that pregnancy, with increased amounts of adrenal corticosteroids, might make these patients particularly prone to hypokalemia, but, if this is true, the fact that these women did not respond to supplementary administration of potassium is surprising. Moreover, despite the difficulty in demonstrating low potassium content, a larger percentage of those patients with weakness would be expected to show either serum or electrocardiographic change than has actually been the case. Finally, as has been noted, the kaliuretic effect in animal experiments was the same for both chlorothiazide and hydrochlorothiazide, casting further doubt on the role of potassium in the production of weakness with chlorothiazide or the lack of weakness with hydrochlorothiazide. Whatever the cause, hydrochlorothiazide appears to hold an advantage in this respect.

Intravenous Administration.—Twelve patients received hydrochlorothiazide intravenously, with 50 mg. in 5 ml. of distilled water injected once a day and given again two to four times at two-day intervals in 8 of these 12 patients. Loss of weight 24 hours after administration ranged from 2 to 8 lb. (0.9 to 3.6 kg.), and a reduction of 1+ to 2+ in peripheral edema was noted. Administration by this method is fairly convenient and appears efficacious when parenteral administration is required.

Summary

In 83 patients, hydrochlorothiazide (Hydrodiuril) was substituted for chlorothiazide with relative ease and the edema-free, "compensated" status was maintained with dosages approximately one-tenth those of the latter compound. In 17 patients who had not received chlorothiazide, hydrochlorothiazide produced the same beneficial results as would be expected from chlorothiazide. Hypertensive patients without clinical congestive failure

showed improvement both symptomatically and by fall in blood pressure. In patients requiring parenteral administration, intravenous administration of hydrochlorothiazide is convenient and effective therapy. The most important advantage appears to be the lack of weakness in patients receiving hydrochlorothiazide.

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The hydrochlorothiazide used in this study was supplied as Hydrodiuril by Merck Sharp & Dohme, Inc., division of Merck & Company, Inc., Philadelphia.

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HEMORRHAGE FROM MULTIPLE SITES ASSOCIATED WITH CHLORPROMAZINE-INDUCED JAUNDICE

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Hemorrhage occurs rarely during medication with chlorpromazine, and then usually as purpura, without jaundice. Jaundice occurs more commonly; its estimated incidence is 1 to 2%. However, hemorrhage and jaundice can appear together during administration of the drug. A 66-year-old woman had been taking 75 mg. of the drug for 17 days when the yellow color of her skin was first noticed. Three days later she bled spontaneously from the vagina, rectum, and urinary tract, and ecchymotic areas appeared in the skin of the knees. Hypoprothrombinemia due to a toxic action of the drug was considered the cause of the hemorrhage and was corrected promptly by vitamin K, therapy; the jaundice secondary to the chlorpromazine-induced hepatitis persisted into the fourth week.

Chlorpromazine, first synthesized in 1951 in France, where it was introduced as an adjunct to anesthesia, has been available in the United States since May, 1954. It has been used for many purposes but mainly to allay neuropsychiatric disorders, to control nausea and vomiting of varied causes, to overcome hiccups, and to diminish intractable pain.

Its side-effects include excessive dryness of the mouth, drowsiness, tachycardia, depression, nasal stuffiness, and a Parkinsonian type of gait and tremor. Distinct from these side-effects are toxic effects, of which the main ones are fever, maculopapular skin eruption, agranulocytosis, and, lastly and probably most important, jaundice.

The incidence of jaundice is difficult to assess accurately. It is approximated as between 1 and 2% when large separately reported [1] series of cases are added together. After five years of its use in the United States, its manufacturer estimated that more than 13 million people had received the drug. Its widespread use continues and the literature is now studded with reports of resulting jaundice and even of cases of liver involvement without clinically detectable jaundice.[2]

With but one exception thus far, no major or minor bleeding has been reported in association with jaundice after use of the drug. The exception is the third of the three cases reported in 1955 by van Ommen and Brown.[3] This patient bled, presumably from a duodenal ulcer. As in most reported cases the prothrombin time was normal.

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Among the reports of cases in which there was no jaundice associated with chlorpromazine administration, there are four references to hemorrhagic manifestations. Mullins and associates [4] mention purpuric manifestations among the skin eruptions observed in a series of 85 patients, specifically citing the observation of petechial eruptions in two patients. Platelet counts were normal. Childers [5] reported the development of nonthrombocytopenic purpura in

two cases. Prothrombin activity was not significantly prolonged (recorded as 78% of normal in one case and 75% in the other). Marley [6] referred to nonthrombocytopenic purpura in one patient who manifested no other bleeding abnormality. Giacobini and Lassenius [7] reported on 147 patients, observing epistaxis in 7, gingival and uterine bleeding in 2, and conjunctival hemorrhage in 2.

Almost without exception, the prothrombin time has been found to be normal or near normal in the patients with hepatitis induced by chlorpromazine.[8] The sole possible exceptions known to us are reports of two jaundiced male patients in whom the respective prothrombin determinations were recorded as 45% and 62% of normal.[9] In neither instance was bleeding described. (Bleeding is ordinarily not encountered even at these levels of prothrombin activity, which generally correspond to times of 16 to 18 seconds.)

Because of the rarity of the occurrence of any bleeding tendency in conjunction with chlorpromazine therapy and its even greater rarity in the presence of jaundice so induced, the following case is reported as an instance of bleeding from numerous sites (skin, rectum, vagina, and urinary tract) in association with jaundice induced by chlorpromazine ingestion. The rectal hemorrhage was massive; the other bleeding was relatively subdued. No cause for the bleeding was elicited other than that associated with the drug-induced jaundice.

Report of a Case

A 66-year-old woman was admitted to Beth Israel Hospital on April 2, 1958, with a chief complaint of yellow color of the skin of three days' duration. The patient had presented herself to the outpatient department on Feb. 5, 1958, with a three-week history of nausea, constipation, and mild abdominal pain. She subsequently attended both the mental health and gastrointestinal clinics. Sigmoidoscopy and roentgenographic examination of the colon showed normal results. Seven weeks prior to admission to the hospital she had been placed on therapy with reserpine and meprobamate with little relief of her symptoms. Three weeks prior to admission the medication was changed to 25 mg. of chlorpromazine, three times daily, by mouth. Three days prior to admission the patient noted the onset of the yellow color of her skin. When this persisted she consulted a local physician who referred her to the hospital.

The patient had not observed the color of her stools but had noted increasingly dark urine with the onset of jaundice. Her appetite was good. There was no history of pruritus, skin eruption, fever, melena, or hematuria. Three days prior to admission she had removed a pessary, worn for uterine prolapse and cystocele. After its removal, she had noted slight bleeding similar to that which had occurred on previous occasions.

The patient had a history of mild hypertension for six years, treated at times with reserpine. A thyroidectomy had been performed 25 years before for hyperthyroidism. The family history and review of systems were essentially noncontributory.

Physical examination revealed a well-developed and well-nourished female in no acute distress but grossly icteric. She was lucid and cooperative. The pulse rate was 80 per minute, blood pressure 150/80 mm. Hg, and temperature 100 F (37.8 C). Marked icterus of both scleras and fundi was observed. No lymph nodes were palpable. The lungs were clear to auscultation and percussion. The heart revealed a grade 2 apical systolic murmur. The abdomen was soft. A smooth nontender liver edge was palpable 3 cm. below the right costal margin. Trophic skin changes and varicosities were evident on the lower extremities. Irregular and macular ecchymotic areas 2 to 3 cm. in size were noted over both knees. Rectal examination showed negative findings. Digital pelvic examination revealed only prolapse and cystocele.

On admission of the patient the hemoglobin level was 13.2 Gm.%, with a hematocrit value of 37%. The white blood cell count was 6,800 per cubic millimeter, with a normal differential count. A catheterized urine specimen revealed a specific gravity of 1.012, with 10 to 15 red blood cells per high-power field and presence of bile (3+) with no increase in urobilinogen.

Several hours after admission the patient passed a few large blood clots from the vagina. Immediate reexamination with speculum by the consultant gynecologist revealed several small bleeding erosions of the vagina at the site of the previously worn pessary. The vagina was packed and the patient appeared comfortable. Twelve hours later (about 2 a. m., April 3, 1958) the patient suddenly had two grossly bloody bowel movements consisting of approximately 700 cc. of dark red blood mixed with clots. Examination at this time demonstrated a blood pressure of 80/60 mm. Hg and a pulse rate of 100 per minute. An infusion of 5% dextrose in water was begun. Before any blood replacement was started the pressure rose to 130/70 mm. Hg. Because of the multiple bleeding sites (skin, vaginal, urinary, and rectal) the possibility of prothrombin deficiency was considered. An emergency blood specimen was taken at this hour for prothrombin time determination to be done later that morning. Fifty milligrams of vitamin K_1 oxide was then administered intravenously. (Due to technical reasons this blood specimen drawn on emergency basis for prothrombin time determination was not suitable for evaluation in the morning.) Proctoscopic examination revealed an ulcerated bleeding hemorrhoid, the area around which was packed with absorbable gelatin sponge. No major recurrence of bleeding from any site was observed

thereafter, but minor bleeding did continue for several days as evidenced by microscopic hematuria, rectal ooze, and positive tourniquet test.

The hemoglobin level was 9.2 Gm.% on the morning of April 3, 1958, and the hematocrit value was 24%. The prothrombin time (Quick) on a blood specimen drawn at 9 a. m., April 3, 1958, was 14.1 seconds, with a control of 12.8 seconds. The white blood cell count was 7,450 per cubic millimeter, with a normal differential count. The bleeding time was 3 minutes, coagulation time 9 minutes (Lee-White), and clot retraction time one hour. The platelet count was within normal limits. The fasting blood sugar level was 183 mg.%. The serum bilirubin value was 11.9 mg.%, the thymol turbidity 2.1 units, and the cephalin flocculation a trace at 48 hours. The alkaline phosphatase level was 10.7 Bodansky units, the total cholesterol level 290 mg.% and the cholesterol esters 150 mg.%. The serum glutamic oxalacetic transaminase (SGO-T) value was 73 units.

A chest roentgenogram showed a mild scoliosis with slight enlargement of the heart, pleural adhesions, and apical fibrotic changes. Roentgenographic examination of the esophagus, stomach, and small and large intestine was within normal limits. The gallbladder was well visualized with excellent contractility after a fatty meal. An electrocardiogram showed evidence of a left ventricular strain and hypertrophy. A liver biopsy was performed on the 37th hospital day, but insufficient tissue was obtained for diagnosis. Oral glucose tolerance tests performed on the 7th and 39th hospital days demonstrated a distinct diabetic curve.

Except for a low-grade fever, with temperatures to 100.5 F (38 C), attributed to a chronic cystitis secondary to her cystocele, the patient made an uneventful recovery. On the third hospital day the urine was free of red blood cells, and by the end of the first week all vaginal and rectal bleeding had ceased. No blood replacement was necessary. The patient was prescribed a full diet of 325 Gm. of carbohydrate, 120 Gm. of fat, and 150 Gm. of protein daily, which she consumed voraciously almost from the beginning of her hospital period. In addition she was given therapeutic vitamins daily and a tablet of ferroglycine sulfate complex three times daily.

At the end of the patient's first week in the hospital, the hematocrit value had slowly risen to 30%. The serum bilirubin level reached a maximum of 19.9 mg.%, with 8.2% direct fraction. The cholesterol (total) level rose to 410 mg.%; the alkaline phosphatase level was 19.4 Bodansky units. The SGO-T value decreased to 50 units, and both cephalin flocculation and thymol turbidity remained normal.

By the second week all evidence of ecchymosis had disappeared. The patient was permitted out of bed on the 21st day, and by the 28th day clinical evidence of jaundice had disappeared. Proctoscopy just prior to discharge revealed complete healing of the eroded hemorrhoid. On the 42nd day after admission the patient was discharged to the clinic, where she was followed for three months with no recurrence of jaundice or evidence of further bleeding.

Comment

There can be little doubt concerning the basic diagnosis of chlorpromazine-induced jaundice. The clinical appearance of jaundice on or about the 17th day of drug ingestion is typical. The chemical laboratory data are equally typical, showing hypercholesteremia and hyperphosphatemia (alkaline) with normal flocculation tests and relatively little rise in the SGO-T level. The degree of hyperbilirubinemia (up to 19.9 mg.%) is well within the zone attained when jaundice is associated with this drug.

The hyperglycemia appeared to be an independent finding related to a coincidental occurrence of diabetes mellitus. The peripheral blood findings (normal white blood cell count with minimal polynucleosis) is quite compatible with this diagnosis. The frequent finding of eosinophilia was not fulfilled in this instance. Biopsy of the liver, not attempted until the 37th day in the hospital, unfortunately was of no practical assistance because of the insufficient tissue obtained. It is entirely possible, of course, that by this time the histological picture might no longer have been diagnostic or even abnormal.

A striking observation by the medical attendants in this case was the appetite manifested by this patient almost from the first days in the hospital, when the bleeding had quieted down and feeding by mouth was resumed. It was a situation which evoked considerable comment by physicians and nurses: she fairly leaped at her tray and devoured all food in sight rapidly, uninterruptedly, and completely. This could hardly be explained by her history of thyroid disease, and she was found to be euthyroid in the current period of hospitalization. We had not observed this in previous cases of chlorpromazine-induced jaundice, nor does the literature remark on it.

Nothing resembling this excessive hunger and appetite is ordinarily observed in hepatitis of viral origin. Occasionally in the recovery stage of acute viral hepatitis, excessive food intake becomes a problem in the future management of the patient because of the tendency to rapid and extreme weight gain [10] but is ordinarily not seen from the peak of the illness. However, in our experience with chlorpromazine-induced jaundice, it is highly characteristic to observe relative well-being almost from the onset of the illness. Disproportion exists between the depth of the jaundice and the relative lack of discomfort and complaint by the patient, with the possible exception of pruritus early in the illness.

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Hemorrhage is an exceedingly rare manifestation of chlorpromazine-induced hepatitis with jaundice, as has already been pointed out, and is only slightly less infrequent in the patient receiving this drug who does not develop jaundice. In our jaundiced patient the bleeding appeared from four sites, being of major importance from the rectal mucosa and less prominent in the vagina, the urinary tract, and skin over the knees. The cause is not absolutely clear, but in the absence of a more satisfactory alternative explanation a likely one is hypoprothrombinemia. Absolute proof of the existence or lack of existence of such hypoprothrombinemia at the onset of hemorrhage is lacking because of the unfortunate technical deficiency in handling the blood sample drawn soon after the occurrence of the rectal hemorrhage and prior to the administration of the vitamin K_1. About seven hours had elapsed by the time another sample of plasma had been obtained for prothrombin time determination. The reading was then 14.1 seconds with a control of 12.8 seconds. Twenty-four hours later it was 13 seconds, equal to the control.

When vitamin K_1 is administered intravenously, bleeding is usually controlled within 3 to 6 hours, and a normal prothrombin time (if previously markedly elevated, enough to initiate hemorrhage) may often be obtained within 12 to 14 hours. It cannot be concluded beyond question that the assumed plasma prothrombin diminution was thus restored toward normal by the vitamin K_1. Nonetheless, it is tempting to make this assumption because of the later (secondary?) rise in prothrombin time to 16 seconds, when next tested a week later on the 11th hospital day. However, it is recognized that seven hours is ordinarily too brief a period in which to anticipate a considerable reduction in the prothrombin time by means of vitamin K therapy, although it may occur.

The mechanism whereby such reduction of prothrombin time might have been accomplished by parenterally given vitamin K_1 is not fully clear. Generally it is felt that the hepatic involvement due to chlorpromazine is a result of a sensitivity reaction with consequent interference with the normal flow of bile from liver cell to bile radicle. In viral hepatitis, toxic hepatitis, and other diseases in which the parenchyma of the liver is diffusely injured or destroyed, the reduced plasma prothrombin content responds little or not at all to vitamin K. On the other hand, in case of biliary obstruction or of bishydroxycoumarin-induced reduction of plasma prothrombin content, the effect of parenterally given vitamin K is to correct the prothrombin deficiency.

Thus, if a reduced prothrombin content in the blood was counteracted or corrected by vitamin K_1 in our case, it is fair to conclude that the inflammatory reaction in the liver due to chlorpromazine must differ from that occurring in viral hepatitis. This conclusion is supported by our knowledge of the difference in the histology of the liver in these two disease states.

It should be stressed that in diseases of the liver there are factors in blood coagulation other than prothrombin, such as proconvertin (factor VII) and accelerator globulin (factor V or proaccelerin). Our measurement of prothrombin time by the Quick method does not delineate the respective roles and presence of these additional factors.[11] All these factors affect the prothrombin time, and when we demonstrate a deficiency in prothrombin we cannot be certain which is at play.

In the face of the jaundice, in the absence of recognition of any other factor promoting bleeding, such as platelet deficiency, and in view of the rapid cessation of bleeding on administration of vitamin K_1, we are inclined to believe that hypoprothrombinemia was the cause. It has already been pointed out that this is an extremely rare finding in the experience of those who have measured prothrombin activity in chlorpromazine-induced hepatitis. The few instances of bleeding associated with the use of chlorpromazine have been mild and observed almost exclusively without the development of jaundice. The rarity of this occurrence is the reason for recording this experience.

Summary

A 66-year-old diabetic woman bled from multiple sites (rectum, vagina, urinary tract, and skin) in association with jaundice induced by chlorpromazine, administered for 17 days. The likely explanation for the hemorrhage is hypoprothrombinemia, although there is a possibility of defects in other coagulation factors. Note is taken that depressed prothrombin activity after chlorpromazine ingestion is uncommon. Hemorrhagic manifestations in association with the administration of chlorpromazine are rare. Particularly is this infrequent in reported cases of jaundice. Minor bleeding has been noted in the absence of jaundice, usually in the form of purpura. A striking clinical observation in this patient was the voracious appetite she manifested from the height of her illness.

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OTOTOXICITY OF KANAMYCIN

REPORT OF THREE CASES

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Severe and apparently permanent loss of hearing was observed in three patients who received kanamycin in the treatment of serious infections. One man, aged 46 years, received 40 Gm. in the course of 16 days; another, aged 62, received 14 Gm. in the course of 7 days. In these cases tinnitus preceded the impairment of hearing. A woman aged 55 received 14 Gm. in two courses separated by an interval of five days. In her case there was no warning tinnitus. In all cases the deafness progressed after administration of the kanamycin was stopped; loss of hearing has been practically complete, and no improvement has been found at later examinations.

The new antibiotic kanamycin, discovered by Umezawa in 1957, is still under clinical observation, and we believe that all serious toxic effects should be reported in order to establish its uses and limitations. This is necessary in the study of any new antibiotic, inasmuch as these are frequently coming on the market.

Report of Cases

CASE 1.—A 46-year-old man was admitted to the hospital because of hematemesis of 24 hours' duration. About 15 years previously the patient had had paratyphoid. Two years ago he was operated on because of a hernia of the nucleus pulposus, with good results.

Present Illness.—The patient stated that about five years previously he began to notice epigastric discomfort two to three hours after meals; this was relieved by taking food or antacids. The pain became worse and was so severe that the patient was awakened at night. His physician treated him for peptic ulcer, in spite of negative findings of roentgenographic study. He improved with this medication, although he said that he had periods of pain in the same area which were rapidly relieved by taking antacids. After the treatment he had another series of roentgenographic studies of the stomach and again the findings were normal.

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Two years before the present admission, when he had been in Johns Hopkins Hospital for an operation on the spinal column, the patient had another roentgenographic study and for the first time was told that he had a healed duodenal ulcer. The roentgenogram showed a deformity of the duodenum.

He felt all right until three months before admission, when he again had epigastric pain, relieved by taking food or antacids. Twenty-four hours before admission the patient felt weak and noticed black stools for the first time. Four hours before admission he felt extremely weak and dizzy, vomited blood, and became very pale. A physician was called and found him in mild shock; he was therefore referred to the British American Hospital for further treatment.

Physical Examination.—On admission the patient was pale, perspiring profusely, and somewhat nervous. His blood pressure was 80/40 mm. Hg, pulse 120, and respirations 24 per minute. The physical examination was noncontributory except for signs of mild shock. He immediately received a blood transfusion. In two and one-half days he received a total of 2,000 cc. of blood, after which the hematocrit fluctuated between 25 and 26%, and the hemoglobin concentration between 8.26 and 8.58 Gm.%. More transfusions were given until the hemoglobin value became 11.74 Gm.% and the hematocrit 38%, so that he could be operated on on his third hospital day.

An extensive gastrectomy (Hofmeister-Finsterer) was performed. By the time the patient returned to his room the hemoglobin level was 11 Gm.% with a hematocrit of 39%. The patient then received 1 Gm. of oxytetracycline intravenously for three successive days, during which period his temperature fluctuated between 99 and 100 F (37.2 and 37.8 C). It became normal on his fourth postoperative day, and the antibiotic therapy was discontinued. He was doing well except for the pulse, which remained between 100 and 110 per minute. The laboratory studies before the operation showed normal coagulation, bleeding, and prothrombin times. Blood urea level was 48 mg.%, the urine was normal, and the serologic examinations gave negative results. His blood was type O, Rh-positive.

Twenty-four hours after the antibiotic therapy was discontinued, on the fifth postoperative day, the patient had a chill and his temperature rose to 103 F (39.4 C); the pulse was then 140 and respirations 30 per minute, and blood pressure was 120/80 mm. Hg (fig. 1). The white blood cell count was 17,000 per cubic millimeter, with 86% neutrophils. Results of two blood cultures taken on that day and the following day were negative. Urine examination also gave a negative result. Blood urea nitrogen level was 46 mg.%. The patient was then given crystalline penicillin, 500,000 units every six hours. His temperature improved with this therapy, but the patient's condition remained toxic; the pulse was 110 and 120 per minute. It was then evident he was suffering from a severe infection. The white blood cell count had increased to 20,000 per cubic millimeter, with 83% neutrophils. On the ninth postoperative day, because the patient continued with severe tachycardia, tachypnea, fever, and vomiting for 48 hours, it was decided to use kanamycin (Kantrex). The first day he was given 1 Gm. but from then on a total of 3 Gm. per day was given for 12 days. When he complained of tinnitus the kanamycin dosage was reduced to 1 Gm. a day for the next three days. He received a total of 40 Gm. over the period of 16 days.

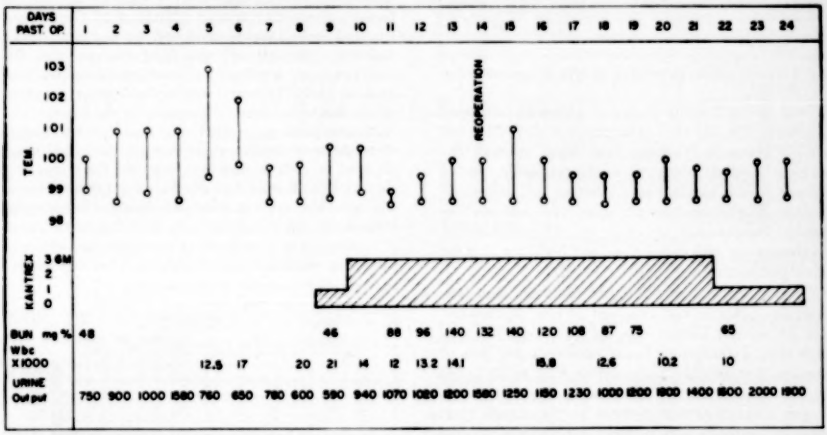

Fig. 1 (case 1).—Chart showing temperature, urinary output, blood urea nitrogen level, and white blood cell count in relation to administration of kanamycin (Kantrex).

During the administration of the antibiotic daily urine examinations were carried out, but no major damage to the kidney could be detected. The hematological values became normal and the elevated blood urea nitrogen level, which was interpreted as indicating prerenal azotemia, dropped gradually. On his 10th postoperative day, 24 hours after kanamycin therapy had been started, the surgical wound began to drain profusely, and a culture of the exudate was positive for coagulase-positive Staphylococcus pyogenes var. aureus. This staphylococcus was sensitive to chloramphenicol, erythromycin, and kanamycin and resistant to eight other antibiotics.

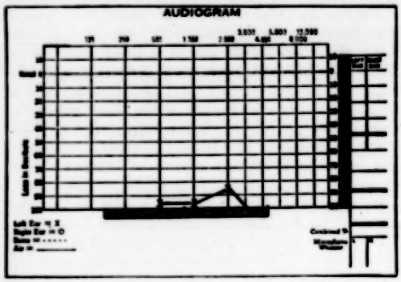

Fig. 2 (case 1).—Audiogram taken on 17th postoperative day.

On the 12th day of administration, the 22nd hospital day, after he had received 37 Gm. of kanamycin, he started having ringing of a high pitch in both ears. Twenty-four hours later he noted loss of hearing that rapidly increased so that in 48 hours he "heard nothing." The nasal mucosa was reddened, there was pus present in the tonsils, and bilateral cerumen was washed out. Both eardrums were retracted and a whitish deposit was noted at the posterior superior quadrant of the left eardrum. An audiogram made at this time (fig. 2) showed severe bilateral deafness. There was no discrimination whatsoever in hearing for speech even at 100 db. in either ear. On his 14th postoperative day the patient was taken to the operating room, the wound was reopened, and a large subhepatic abscess was found and drained. After this the patient's pulse and temperature gradually came down and his condition improved until his discharge after 30 days in the hospital.

There was no history of the patient's ever having received streptomycin or neomycin. The pathologist's report on a specimen from the stomach was hemorrhagic gastritis; no ulcer was found. The patient's progress has been followed for two months and he has been symptom-free from the gastrointestinal point of view, but the damage to the eighth nerve has continued, with total deafness (fig. 3).

Case 2.—A 62-year-old man came into the hospital because of urinary infection and renal failure. He had had repeated attacks of urinary infection since childhood, with several attacks of renal lithiasis. He had undergone a nephrectomy because of renal stones 12 years previously. He had been known to be hypertensive for the past three years.

Present Illness.—About four weeks before admission he developed a severe epistaxis, requiring posterior packing of the nose and surgical cauterization of the mucosa. His blood pressure was 200/130 mm. Hg, and the blood urea nitrogen level was 170 mg.%. Because urine culture gave a positive result he was given nitrofurantoin (Furadantin), with poor results, and then 1 Gm. of kanamycin twice a day. He received a total of 14 Gm. When the patient had received 12 Gm. he began to notice tinnitus, and although the drug therapy was discontinued he developed almost complete deafness in four days. Hearing was normal prior to treatment. Pus was found on pressure of the tonsils, and both eardrums were thickened and whitish. Crusts were present in the right nostril. An audiogram showed a severe hearing loss for the right ear (fig. 4), but an island of decibels for 1,000 cycles in the left. The patient received, besides kanamycin, vitamin K and a lipid-protein thromboplastic agent (Clauden) as the only other medicaments. He denied any previous ear trouble or ever having received streptomycin or neomycin.

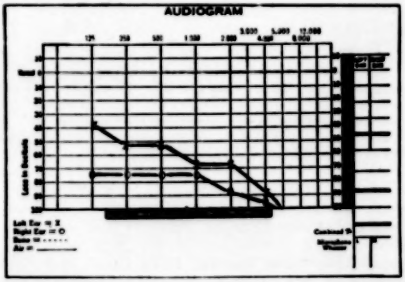

Fig. 3 (case 1).—Audiogram taken eight days after therapy with kanamycin was discontinued.

Physical Examination.—The patient looked ill, and his mucous membranes were pale and dry. Lungs were normal to percussion and auscultation. The heart was normal and blood pressure was 200/110 mm. Hg. The laboratory tests made on admission showed hemoglobin level to be 7.62 Gm.%; red blood cell count, 2,610,000 per cubic millimeter; white blood cell count, 6,950 per cubic

millimeter, with eosinophils 6%, neutrophils 74%, lymphocytes 13%, and monocytes 7%. The red blood cell count showed some polychromatophilia and anisocytosis. Coagulation time was 8½ minutes, bleeding time 1 minute. His blood was type O, Rh-positive. The blood urea nitrogen level on admission was 86 mg.% and blood creatinine level, 5.1 mg.%. Serologic examination gave a negative result. Urine showed a specific gravity of only 1.005; there was 2+ albumin and the sediment showed white and red blood cells with occasional granular casts. The urine culture was positive for Staph. aureus, coagulase-positive and sensitive to chloramphenicol, novobiocin, and tetracycline but resistant to other antibiotics. The electrocardiogram showed slight abnormality which was interpreted as consistent with an elevated serum potassium level.

Course in Hospital.—The patient remained in this hospital for one week. He showed a daily low-grade fever and his blood pressure fluctuated between 160/100 and 200/110 mm. Hg. He received a transfusion of 500 cc. of blood and a 250-mg. dose of chloramphenicol every six hours. He was discharged slightly improved. When seen four months later he had severe signs of uremia and the deafness had continued with the same intensity.

CASE 3.—A 55-year-old woman stated that three months before admission she had begun to vomit and had epigastric distress without relation to food or time of day. When the attacks of vomiting recurred a physician found that she had hypertension. During the past six years she had had some dyspnea on exertion, and she had noted loss of weight in the past six months. We were unable to obtain a history of her having received streptomycin or neomycin.

Physical Examination.—On admission to hospital the patient was obese; her skin was dry and there was edema of the eyelids as well as the ankles. The blood pressure was 170/100 mm. Hg. The blood sugar level, which had been 230 mg.% two months before admission, was 105 mg.%. Blood urea nitrogen level was 68 mg.%. The urine showed a few leukocytes, red blood cells, and granular and hyaline casts. A urine culture was reported positive for Escherichia coli, sensitive to nitrofurantoin, kanamycin, chloramphenicol, and tetracycline.

Course in Hospital.—On her sixth hospital day, because of positive urine culture, she received 2 Gm. of kanamycin, then 1 Gm. each day for the next six days. The urine culture remained positive and on her 18th hospital day kanamycin therapy was resumed, 2 Gm. the first day and 1 Gm. on the three successive days. After receiving a total of 14 Gm. she complained of deafness, and, although the drug therapy was discontinued immediately, she rapidly developed total deafness. The audiogram was reported negative for both ears in air as well as bone conduction.

Comment

It is known that neomycin is nephrotoxic and neurotoxic [1] and that kanamycin has a similar chemical structure and similar antibiotic behavior, since there is complete cross-resistance between the two antibiotics [2]; therefore it seemed quite possible that kanamycin would be toxic for the kidney as well as for the ear. It is interesting that kanamycin has an incomplete cross-resistance with another neurotoxic antibiotic, streptomycin. The literature indicates that kanamycin has a definite toxicity for animals [3] as well as for man, producing damage to the kidney,[4] affecting the tubular and glomerular function,[5] and damaging the eighth cranial nerve.[6] At present the exact toxic dosage of kanamycin has not been established, but it seems to depend not only on the total amount administered but also on the dose given per day.

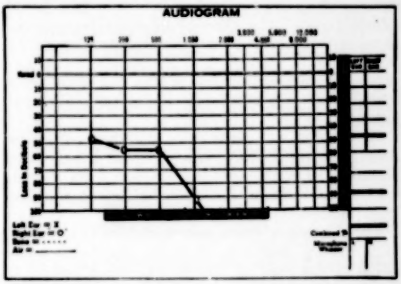

Fig. 4 (case 2).—Audiogram taken two weeks after therapy with kanamycin was discontinued.

Bunn and Baltch,[7] reporting on 15 patients, observed no side-effects from kanamycin when 1 Gm. was given daily for 3 to 17 days. The same authors observed the toxicity to be of a minimal order when the drug was given for less than three weeks in doses that varied between 0.5 and 3.0 Gm. per day. Above this level they observed eosinophilia, urinary abnormalities, and damage to the eighth nerve, particularly when the total amount of kanamycin received by the patient was between 40 and 50 Gm.[4a] Other investigators [8] report no toxic effects with daily doses of 1 to 2 Gm., but if the time of administration is prolonged to six months, even though the daily dose is reduced to 0.5 Gm., damage to the auditory nerve is produced.[4b] Donomea [4c] found audiometric impairment in 20% of the patients who received over 6 Gm. of kanamycin per week, but he was able to reduce this toxicity to 4% if the amount of the antibiotic was less than 6 Gm. per week.

In our report, in case 1, kanamycin was administered in the maximum recommended dose. The patient had a prerenal azotemia, as proved by the

return of the blood urea nitrogen level to normal values. As soon as the intra-abdominal abscess was drained, and while the administration of kanamycin continued, there was no decrease in the urinary output and the blood creatinine level remained normal. The total amount of kanamycin that the patient received was 40 Gm. in 16 days, and the symptoms of injury to the eighth nerve appeared when he received 37 Gm.; therefore, the ototoxicity became evident before the level that has been pointed out as toxic was reached.[7]

In the other two cases presented here serious renal lesions existed before the administration of kanamycin. In case 2 the total amount of kanamycin given to the patient was 14 Gm. in seven days, with impairment of hearing becoming evident after he had received 12 Gm. In case 3 the damage seemed more marked, since the total amount of the antibiotic was only 14 Gm., administered in two periods, with an interval of five days of no kanamycin administration. The signs of deafness became noticeable during the second course of treatment with only 4 Gm. of kanamycin. This last case is suggestive of a hypersensitivity to the antibiotic or a cumulative toxic effect due to the patient's renal failure.

Common to our three cases was the progressive damage to the auditory nerve, which appeared to be irreversible and which continued even though kanamycin therapy was discontinued at the first signs of damage.

The number of cases presented here is too small to permit conclusions to be drawn, but the accumulation of this type of information should establish the position of this new antibiotic in clinical practice and clearly determine its limitations.

Apartado 2713 (Dr. Garrido Lecca).

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HAZARDS OF MERCY.—From time to time reports appear in the newspapers of what are described as "Mercy Flights." They are usually undertaken to convey someone from an outlying area to a larger centre where he can obtain urgently needed special medical attention or to rescue someone in danger of his life, for example, from flood. A number of such flights have ended in disaster, perhaps with loss of the lives of all concerned, and no doubt many people have wondered what lay behind these tragedies. . . . Since the majority of Mercy Flights intimately concern members of the medical profession, it is vital that they should understand what such flights involve and the conditions under which they may be undertaken. . . . While medical emergencies can arise at any time, the aircraft mostly used in this work can be flown with normal safety only in daylight and fair weather. Most medical or ambulance flights take place under visual flight conditions and are perfectly normal operations with an excellent safety record. It is the minority which become Mercy Flights that constitute the problem. The difficulties outlined here could be reduced by an understanding on the part of the doctor of the pilot's problems, and by a readiness to discuss with the pilot the medical aspects of a flight proposed at night or in bad weather—that is, by definition, a Mercy Flight. —Mercy Flights and Their Safety, editorial, *The Medical Journal of Australia*, Jan. 24, 1959.

CONSCIOUSNESS AND PAIN DURING APPARENT SURGICAL ANESTHESIA

REPORT OF A CASE

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and
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A patient underwent an operation under general anesthesia which included the use of succinylcholine and intravenously given lidocaine, with assisted respiration. After recovery she gave evidence of having been intermittently conscious during the three-hour period of supposed anesthesia and stated that she had suffered extreme pain during much of the operation. An awareness that such an extreme in pain reflex threshold may rarely exist in patients undergoing operative procedures should caution us to be more appreciative of the subtle signs suggesting an inadequate state of anesthesia. This is particularly applicable when respiratory reflexes and other types of response are obviated by the use of neuromuscular blocking agents.

The introduction of curare as a neuromuscular blocking agent in clinical anesthesia by Griffith and Johnson [1] in 1942 set the stage for radically different concepts in the practice of surgical anesthesia. Here was a means whereby satisfactory anesthesia could be offered to the most demanding of surgeons without the necessity of maintaining high blood and brain tissue levels of inhalation or intravenous anesthetic agents. The demonstration by Foldes and co-workers [2] of the close control of neuromuscular paralysis afforded by a continuous infusion of dilute succinylcholine gave more widespread popularity to and promoted acceptance of this school of practice. In 1955 Artusio [3] introduced the technique of ether analgesia and described the homeostatic benefits derived by maintaining a level of anesthesia at which the patient was capable of responding to questions and of discriminating subjective senses of taste and color.

The combination of minimal central nervous system narcosis plus neuromuscular blockade has received increasing acceptance by clinical anesthesiologists throughout the United States and abroad during the past 10 years. We have utilized this form of anesthesia in several thousand surgical and gynecologic operations and have been favorably impressed with it as a technique providing a smooth course of surgical anesthesia, with a minimum of side-effects and a short postoperative waking time. After such an anesthetic procedure there occurred recently on our service a complication which brought forcibly to our attention a potential hazard involved in this concept of anesthesia, which we feel is of sufficient importance to be reported.

Report of a Case

The patient was a 40-year-old woman who entered the hospital with the diagnoses of cystocele and rectocele. She was scheduled for a vaginal hysterectomy and an anterior and posterior colporrhaphy. Her operative history included a tonsillectomy as a child and an appendectomy at the age of 16 years, both under gas-oxygen-ether anesthesia. She had had four vaginal deliveries. For the first three of these she had had gas-oxygen-ether anesthesia, and for her fourth and last delivery a saddle-block technique had been used. During one of the pregnancies she had been given paraldehyde in an early and quiescent phase of labor, had become agitated, and had had intense and vivid recollections of her pain after this medication. Administration of codeine and meperidine at various other times resulted in extreme episodes of nausea and vomiting. Administration of erythromycin, two years prior to admission, had caused a skin eruption. Three years prior to admission she was hospitalized with a tentative diagnosis of pericarditis, but studies did not confirm this impression and it was decided that the presenting symptoms were emotionally based.

Physical findings on the present admission were normal except for the pelvic and perineal disease for which the operation was to be performed. Her hemoglobin concentration was 11.7 Gm. % (81%), and white blood cell count 6,800 per cubic millimeter with 48% polymorphonuclear cells, 50% monocytes, and 1% basophils. The hematocrit was 38%. Blood glucose level was 86 mg.%, blood urea level 35 mg.%. Urinalysis revealed nothing abnormal; specific gravity was 1.013.

The patient was given, as bedtime sedation the evening before the operation, secobarbital and amobarbital (Tuinal), 100 mg., and perphenazine (Trilafon), 4 mg., each by mouth. In view of her his-

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tory of side-reactions to opiates no narcotic was given preoperatively, the medication consisting of 5 mg. of perphenazine and 0.4 mg. of atropine intramuscularly one hour before the induction of anesthesia. Bearing in mind also the history of recent emotional problems it was decided that a general anesthetic would be indicated for the anticipated operative procedure.

Anesthesia was induced with intravenous administration of thiopental, 200 mg. in a 2% solution. The patient was given a continuous intravenous infusion containing 0.1% lidocaine and 0.025% succinylcholine. Nitrous oxide and oxygen at a 4-liter and 2-liter flow, respectively, in a semiclosed circle-absorber system was then administered under a mask. Respirations were spontaneous but assisted throughout the course of anesthesia. The operative procedure lasted two hours and 50 minutes and the anesthesia three hours and 10 minutes. During this time a total of 400 mg. of thiopental, 500 mg. of succinylcholine, and 2 Gm. of lidocaine were used. A no. 3 oropharyngeal airway was inserted early during the procedure and removed at the end before the patient left the operating room. The systolic blood pressure was 120 mm. Hg before the induction of anesthesia and ranged between 115 and 130 mm. Hg during the entire procedure. The pulse rate ranged from 84 to 100 per minute. The blood loss was appreciably more than usual, and this was commented on by the members of the operating team.

Two 500-cc. units of blood were administered during the operation. The color of the patient and of the blood was good at all times and the anesthesia progressed uneventfully. It was noted that there were occasional episodes of resistance to inspiratory assistance. At one point during the operation the patient (in a lithotomy position) suddenly moved her right leg.

The patient was responding and talking to visitors within 10 minutes of leaving the operating room. Her blood pressure remained a little low during much of the afternoon (88 to 100 mm. Hg systolic), but the pulse was slow and her skin was warm and dry, although she appeared slightly pale. There was little nausea, and no vomiting was noted by the nurse or remembered by the patient during the postoperative period. She received during the first three days a total of 25 mg. of morphine and 10 mg. of perphenazine, in divided doses.

Despite this apparently uneventful anesthetic course the patient had a most unpleasant experience to relate to the surgeon and the anesthesiologist. She had been intermittently conscious and unconscious during the three-hour anesthetic period. She volunteered the information that an airway had been inserted in her mouth and removed at some later time. She reconstructed details pertaining to the discussion of the blood loss and the decision to start administration of the second unit of blood. She also experienced dull, unbearable pelvic, lower back, and perineal pain during much of the operation.

Comment

There is little doubt in the minds of the attending physicians that the patient was conscious during phases of this procedure and suffered considerable discomfort. As this was the first such case in our experience, we have reviewed critically the management of the entire anesthetic procedure including the preanesthetic medication, the agents and proportions used, the mechanical accuracy of the anesthesia apparatus, the background of the patient, and our own ability to evaluate the adequacy of anesthesia under the situation described.

Galla and co-workers [4] have recently reevaluated the traditional signs of anesthesia as they might apply to newer anesthetic agents and techniques. Nearly all of our signs of anesthetic depth are dependent on the muscular response to some type of stimulus, whether exogenous, provoked by the observer, or endogenous, as a result of physiochemical changes at the vital centers. While the patient is under neuromuscular blockade such signs are either eliminated or dampened to the point where they become less easily recognized. Galla and co-workers stressed the importance of two signs indicating light planes of anesthesia in the patient under curare anesthesia. The first of these is increased resistance to inflation of the lungs, which is associated with Courtin and co-workers' electroencephalographic level 1 [5]; the second is pupillary dilatation in response to surgical stimulus. This same author pointed out that alternative etiological factors leading to pupillary dilatation are excessively deep planes of anesthesia and anoxia.

Artusio [3] has demonstrated that in plane 2, stage 1 of ether analgesia, although a patient is still responding to questioning and reacting to surgical stimulus with gross movements, there is complete amnesia on postoperative questioning. Facial grimacing and movements of an extremity are signs frequently seen during analgesic techniques, whether the primary anesthetic agent is nitrous oxide or ether.

In the case described in this report pharyngeal and corneal reflexes were absent, and respirations were depressed to the point of requiring some as-

sistance. These several signs suggested a surgical depth of anesthesia. There was maximal pupillary constriction throughout the course of the anesthesia, which has been a consistent finding in our patients who receive intravenous thiopental, succinylcholine, and lidocaine combined with a nitrous oxide and oxygen inhalation anesthetic, and which would not have suggested an unduly light plane of anesthesia. Any degree of pupillary dilatation would have caused us to be concerned about the adequacy of our ventilating technique or about the possibility of an adverse response of the patient's cardiovascular and cerebrovascular mechanisms to a surgical or an anesthetic insult.

Although the patient was breathing spontaneously throughout the anesthetic course, there were periods of increased resistance to lung inflation while inspiration was assisted and occasional episodes of sudden change in rate and depth of breathing. These phases of her respiratory pattern were the only indications of light anesthesia. In addition, as was noted in the protocol, the patient made a sudden movement of her right leg at the time the surgeon made his initial incision in the posterior vaginal mucosa to repair the rectocele. This occurred 30 minutes before the end of the entire operative procedure. Such a plane of anesthesia was not considered undesirable; it caused no impediment to the surgical procedure and allowed for full compensatory response to the not inconsiderable blood loss being suffered by the patient. With the basal narcosis of intravenously given thiopental and an apparent metering of two-thirds nitrous oxide in a total flow of 6 liters, it was felt that there was no chance that the patient would not receive complete analgesia and amnesia for the operative procedure.

A review of the present case serves to caution us that, in our efforts to make possible surgical intervention with a minimum of homeostatic disturbance, the anesthetic or pain-reflex threshold of the patient may be at such a level that we are actually administering inadequate amounts of depressive agents to obtain the desired degree of analgesia and amnesia. It should be emphasized that signs of unduly light anesthesia may be most subtle and that the analgesic techniques utilized may be accompanied by the inherent risk of a conscious and uncomfortable patient. The use of the neuromuscular blocking agents amplifies the chances of this situation occurring. Perhaps the addition of an opiate to the preanesthetic medication may have sufficed to have given the patient the required amount of basal narcosis. The importance of the preoperative opiate in a nitrous oxide anesthesia has been stressed by Clement,[6] although in recent years much has been written concerning the iniquities of prescribing opiates to the patient going to surgery.[7] A larger dose of thiopental than the 400 mg. used for the three-hour procedure would certainly have been justified and could have induced the additional anesthetic depth necessary. However the deeper anesthesia is accomplished, greater concern when confronted with the signs of light anesthetic planes may help to avert subsequent experiences such as the one just described.

Summary

A patient under apparent anesthesia for a prolonged perineal operation suffered indisputable phases of consciousness and extreme pain. Pertinent aspects of the analgesic techniques in anesthetic management include a consideration of the interpretation of the signs of anesthesia as they might apply to our new anesthetic agents and methods, especially the role of the neuromuscular blocking agents in affecting the signs of anesthetic depth. Although the minimal effect on homeostasis of the newer anesthetic techniques is of recognized value, an awareness of the possibility of an anesthetic experience such as the one described should serve to make us pay greater heed to signs of light planes of anesthesia.

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NAUSEA AND VOMITING IN THE IMMEDIATE POSTANESTHETIC PERIOD

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Factors that might determine the incidence of nausea and vomiting were sought in a study of 1,602 patients recovering from general anesthesia. Vomiting was somewhat less frequent in older patients than in younger ones and much less frequent in men than in women. Comparisons between anesthetics were difficult because the type of operation influenced the choice of anesthetics, but under the conditions of this study the use of ether was followed by a slightly lower incidence of vomiting (23.3%) than was the use of cyclopropane (24.1%). Endotracheal intubation and administration of relaxants had no appreciable effect, but insertion of a gastric tube reduced the incidence of vomiting from 25.3 to 15%.

Every general anesthesia is composed of three parts: induction, maintenance, and emergence or recovery. Many clinical and laboratory studies on the first two phases of anesthesia have been reported, resulting in improvements in anesthetic techniques. Patients can now be anesthetized for surgery considered impossible only a few years ago. These improved results are related to new agents, improved techniques and apparatus, and increased knowledge in the fields of physiology, pharmacology, and chemistry related to anesthesia. In contrast to this, relatively little work has been done in relation to the period of emergence from anesthesia.

The introduction of the postanesthesia recovery room has been a significant advance in postoperative care of the surgical patient. Patient safety has been increased by the presence of specially trained nursing personnel familiar with patient care during this critical period. In 1899 Blumfeld wrote, "A patient's dread of operation is often due more to his fear of anesthesia than to the operation itself." [1] The fear of anesthesia is mostly caused by the anticipation of the unpleasantness of the postanesthesia recovery phase. It matters little to the average patient that he received a skillful anesthesia, requiring possibly several hours of constant vigilance and care in order to provide and maintain normal physiology throughout an operative procedure. Rather, the patient's concern is associated with what he experienced when he regained consciousness, and frequently the difficulties of this period are ascribed to anesthesia.

Dripps [2] observed in 1949 that there was "little significant information on such a commonplace problem as the incidence of nausea and vomiting following the administration of an anesthetic." Because of the many variables involved, such as premedication, anesthetic agent and method of administration, duration of anesthesia, type of operation, and age, sex, physical status, mental status, constitution, and habitus of the patient, the task of studying the postanesthesia recovery is a difficult one. This investigation was undertaken in order to collect more information on this important period.

The study was divided into three major parts: observations related to nausea and vomiting, observations related to the mode of recovery, and observations related to blood pressure. This particular report deals only with the observations concerning nausea or vomiting. All data obtained were analyzed and correlations were made between some of the many variables related to anesthesia and surgery; specifically, the possible relationship between physical characteristics of the patient, age, sex, and body structure, and type and duration of operation.

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Procedure

Special study sheets, composed of two parts, were filled out in conjunction with the anesthesia record of each patient. The first section was completed by the person administering the anesthesia. For classification of the structural type the following criteria of body structure based on Kretschmer's [3] work were used: narrow, slender (leptosome); rounded, chubby (pyknic); muscular, well-developed (athletic); and with grossly abnormal proportions or deviations (dysplasic). These records then accompanied the patient to the recovery room, where they were completed by the recovery room personnel under the supervision of an anesthesiologist. The recovery room nursing staff had no precise knowledge of the objectives of this study, so their observations may be presumed to be unbiased.

Notations concerning nausea and vomiting were based only on objective signs. Vomiting was recorded whenever the expulsive efforts produced even a small amount of material. Nausea was re-

corded when a patient was complaining of a desire to vomit or when expulsive but unproductive vomiting movements were observed. Nausea is a subjective experience which may or may not be associated with vomiting or retching; retching is defined as spasmodic contractions of the respiratory and abdominal musculature without expulsion of any material. We use the term nausea in this paper to designate the two phenomena. The patients were asked no questions related to nausea and vomiting, in order to avoid any suggestion in the matter. The patients were discharged from our recovery room when they were alert, with stable vital signs, and oriented as to time and place. The average time for this ranged from two to three hours.

The completed data sheets were coded and the results reported on IBM cards; these cards were used later for tabulation, correlation, and analysis. Complete observations and data were obtained on 1,602 patients of all ages. Of these 752 were males and 850 were females. Five age groups were used in the study: group 1, aged 10 and under, comprising 152 patients, 101 boys and 51 girls; group 2, aged

TABLE 1.—*Distribution of Anesthetic Agents by Age and Sex of Patient*

Age Groups, Yr.	Thiopental-Nitrous Oxide			Ether			Cyclopropane			Cyclopropane-Ether		
	Total	M	F	Total	M	F	Total	M	F	Total	M	F
11-17	9	6	3	15	11	4	24	16	8	15	11	4
18-49	86	38	48	88	41	47	329	70	259	120	44	76
50-65	99	65	34	108	51	57	162	84	78	108	49	59
over 65	78	57	21	85	47	38	65	29	36	51	30	21
Total	272	166	106	296	150	146	580	199	381	294	134	160

10 to 17, comprising 64 patients, 44 boys and 20 girls; group 3, aged 18 to 49, comprising 623 patients, 194 men and 430 women; group 4, aged 50 to 65, consisting of 483 patients, 250 men and 232 women; and group 5, aged over 65, consisting of 280 patients, 163 men and 117 women.

Ninety-seven per cent of the patients were given premedication with barbiturate and belladonna preparations, usually amobarbital (Amytal) sodium and atropine. Only 3% received an opiate in lieu of or in conjunction with the barbiturate or belladonna. Four anesthetic agents were used: a combination of thiopental and nitrous oxide; ether; cyclopropane; and cyclopropane with ether. Their distribution is reported in table 1.

Duration of Anesthesia.—In 408 patients (153 males and 255 females) the duration of anesthesia was one hour or less; in 479 patients (249 males and 230 females) it was one to two hours; in 287 patients (123 males and 164 females) two to three hours; in 172 patients (74 males and 98 females) three to four hours; and in 104 patients (52 males and 52 females) the procedure took over four hours. Results were analyzed by means of the chi-square test; the following criteria were used for p values: $p<0.01$ considered significant, $0.01<p<0.02$ considered of borderline significance, and $p>0.02$ considered insignificant.

Results

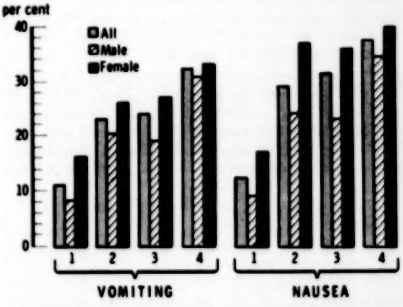
Data concerning patients of age group 1 are included only in the general results (table 2), because we believe that the reactions of children

TABLE 2.—*Incidence of Nausea and Vomiting in Relation to Age and Sex*

Age Groups, Yr.	Vomiting						Nausea					
	Total		M		F		Total		M		F	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Up to 10	54	35.5	34	33.6	20	40.0	57	38.0	36	35.4	21	42.0
11-17	29	45.3	22	50.0	7	35.0	32	50.0	23	52.2	9	45.0
18-49	168	26.9	45	23.0	123	28.6	214	32.7	53	27.3	161	37.4
50-65	97	20.0	37	14.8	60	25.0	112	23.2	39	15.6	73	31.7
Over 65	42	15.0	21	12.5	21	18.0	58	20.7	27	16.5	31	26.5
Total	390	24.3	159	21.0	231	27.2	473	29.5	178	23.7	295	34.5

should not be evaluated with those of adults. Results related to nausea are not reported in several tables for purposes of simplification; results concerning nausea always paralleled those obtained for vomiting.

There was a significant difference in the incidence of vomiting related to anesthetic agents (see figure); for males it was more pronounced than for females ($p<0.01$). The incidence of vomiting (table 2) varied significantly with age, especially



Vomiting and nausea in relation to anesthetic agent used. 1=thiopental and nitrous oxide combination, 2=ether, 3=cyclopropane, and 4=cyclopropane with ether.

in males ($p<0.01$). The incidence of vomiting in males was significantly different from that in females in patients over 11 years of age ($p<0.01$). The incidence of vomiting did not vary significantly with body type (table 3) in either the males or the females ($0.02<p<0.05$ for males; $0.2<p<0.3$ for females). The incidence of vomiting varied significantly with site of operation (table 4) for both sexes ($p<0.01$).

There appeared to be a constant upward trend in the incidence of vomiting as the duration of the procedures increased (table 5), but the incidence was only of borderline significance ($0.01<p<0.02$).

TABLE 3.—*Distribution of Structural Types by Sex and Relation to Incidence of Vomiting*

Structural Type	Distribution				Incidence of Vomiting					
	Total		M	F	Total		M		F	
	No.	%			No.	%	No.	%	No.	%
Leptosome	536	35.5	214	302	103	20.0	31	14.4	72	23.5
Athletic	492	33.9	333	159	122	24.8	81	23.3	41	25.7
Pyknic	396	27.3	88	308	109	27.5	18	20.4	91	29.5

There was a significant relationship between the incidence of vomiting and the presence of a gastric tube ($p<0.01$). Among patients without gastric tubes the incidence was 25.3 and among those with tubes 15%. The incidence of vomiting with endotracheal intubation was 24.4 as against 22% without intubation. With the use of relaxants the incidence was 21.5 and without relaxants 24%.

Comment

A review of the pertinent literature shows that there has been a definite trend in recent years toward a lower incidence of postoperative nausea and vomiting after general anesthesia. Studies reported as recently as 1929 indicate an incidence well above 50 and sometimes as high as 80%.[4] In contrast, Dent and associates [5] reported a low percentage of 27.5 in 1955; Burtles and Peckett [6] 32 in 1957; and Bonica and associates [7] reported a percentage of 30.5 in 1958. Waters [8] reported 40.6% in his study of 1936 but only 35.5% in 1951. In our study the over-all incidences were 24.3% for vomiting and 29.5% for nausea (table 2). It should be pointed out that a number of patients emerged very rapidly from anesthesia, and that some of these patients may have vomited while still in the operating room or on their way to the recovery room. Had these cases been included in the results they would have increased the number of cases of vomiting reported in the recovery room by 15%.

TABLE 4.—*Incidence of Vomiting in Relation to Sex and Type of Surgery*

Site and Type of Operation	No. of Operations			Incidence of Vomiting					
				Total		M		F	
	Total	M	F	No.	%	No.	%	No.	%
Head and neck	135	52	83	44	32.6	14	26.9	30	36.0
Thyroid	37	4	33	17	46.0	4	100.0	13	39.4
Intrathoracic	43	23	20	9	21.0	3	13.0	6	30.0
Intra-abdominal	350	153	197	72	20.5	33	21.3	39	20.0
Biliary tract	97	28	69	22	22.6	10	35.7	12	17.3
Appendectomy	32	15	17	17	53.0	7	46.6	10	60.0
Gynecologic	189	...	189	59	31.2	...	...	59	31.2
Urologic	259	207	52	37	14.2	25	12.0	12	23.0
Peripheral	292	99	193	69	23.3	19	19.0	50	25.9

The anesthetic agent appears to be a factor of major importance in the incidence of postoperative nausea and vomiting (see figure). Results reported in the literature vary widely. Previous reports indicated an 80% incidence associated with diethyl ether anesthesia.[9] In more recent work the trend was lower and averages varied between 30 and 60%.[10] For cyclopropane the results vary between 24 and 50%.[11] Combined thiopental and nitrous oxide has always been reported as giving the lowest incidence, between 14.5 and 30%.[12]

The present study indicates that nausea and vomiting occur in 23.3% of patients receiving ether and in 24.1% of those receiving cyclopropane. The general belief that ether causes more nausea and vomiting than other inhaled anesthetic agents was not substantiated by the results. However, nausea and vomiting after anesthesia with ether are as a rule more persistent than after that with cyclopropane. The incidence after combined thiopental and nitrous oxide anesthesia (11%) was far lower than after any other agent.

The age of the patient (table 2) appeared to influence the incidence of postanesthetic vomiting, particularly in males; for both sexes, however, there was a definite tendency toward lower incidences among older patients. The sex of the patient is a factor of major importance. A higher incidence among females was observed in nearly all circumstances, regardless of the anesthetic agent used. Several other authors have made the same observation.[13]

TABLE 5.—*Incidence of Nausea and Vomiting in Relation to Sex and Duration of Anesthesia*

Duration of Anesthesia, Hr.	Patients, No.			Vomiting						Nausea					
				Total		M		F		Total		M		F	
	Total	M	F	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
1 and under	408	153	255	77	18.8	24	15.6	53	20.7	104	25.0	28	18.3	76	30.0
1-2	479	249	230	104	21.6	44	17.6	60	26.0	132	27.5	48	19.2	84	36.5
2-3	287	123	164	72	25.0	28	22.7	44	27.0	90	31.0	32	26.0	58	35.3
3-4	172	74	98	51	30.0	18	24.3	33	33.6	61	35.4	22	30.0	39	39.8
Over 4	104	52	52	32	32.6	12	23.8	20	38.4	39	37.5	14	26.9	25	48.0

In the site of operation (table 4) has an important role in the relative occurrence of emetic symptoms. This is a generally accepted observation; however, the respective influence of different types of surgery is a controversial subject, especially with respect to intra-abdominal operations.[14] Knapp and Beecher found little difference between intra-abdominal and other operations; Bonica and associates found a high incidence of vomiting after abdominal surgery; Burtles and Peckett found a relatively low incidence; and our results were very low. The divergence of these results obviously indicates that this complex problem is not solved.

Head and neck operations and particularly those on the thyroid were followed by a high incidence of emetic symptoms; this is in accord with the findings of other investigators.[15] The low incidence after operations on the urinary tract, also noted by Burtles and Peckett, is partly explained by the fact that the vast majority of patients undergoing this

type of surgery are men over 50 years of age and partly by the fact that the thiopental and nitrous oxide combination was the anesthetic agent in 52% of the cases.

Several investigators have expressed the belief that the duration of a procedure could influence the incidence of postanesthetic nausea and vomiting.[10] Knapp and Beecher were unable to confirm this opinion. The results obtained in this study (table 5) appear to give some support to it. However, it is necessary before formulating a definite conclusion concerning the influence of duration of anesthesia to analyze certain factors which could bias the results. Different types of operations in relation to duration and age group did not appear to influence the findings. However, the various anesthetic agents do influence postoperative vomiting; consequently, it was important to correlate agent and duration. The distribution of agents used in anesthesias lasting one hour or less was as follows: combined thiopental and nitrous oxide, 135; ether, 28; cyclopropane, 206; and cyclopropane combined with ether, 35. The expected incidence of vomiting calculated for this distribution is 20%; this is very close to the 18.8% obtained in this study. The expected incidence for anesthesias lasting up to two hours is 22.5%; the result of this study showed it to be 21.6%. However, for the longer anesthesias the results were a little above the expected incidence; for anesthesias over three hours, 30 as against 26%, and for those over four hours, 32.6 as against 28%.

The important factor in the analysis is the fact that combined thiopental and nitrous oxide was used in 33% of the anesthesias of one hour's duration, in 22% of those of two hours' duration, in 9% of those of three hours' duration, in 5% of those of four hours' duration, and in only 1% of those lasting more than four hours. This relatively high percentage of thiopental and nitrous oxide anesthesia in the shorter procedures was a factor in the lower average incidence of emesis in these cases. The conclusion is that duration of anesthesia appears to have little influence on the incidence of nausea and vomiting; however, it should be noted that there is an upward trend in the incidence of vomiting as duration increases.

The concept that a gastric tube provides a beneficial effect is substantiated by the data of this study. This has also been the experience of several other investigators. The results in relation to endotracheal intubation and the use of relaxants indicate that these factors have no appreciable influence on postoperative vomiting.

Summary

Observations during the immediate postanesthesia phase were recorded in 1,602 patients. The over-all incidence of vomiting was 24.3%; the incidence in males was significantly different from that in females. The influence of body structure was not marked for either sex, but emesis was less frequent in the older age groups.

Anesthesia with use of combined thiopental and nitrous oxide was followed by vomiting in 11% of the cases. Ether and cyclopropane anesthesia were followed by vomiting in 23.3 and 24.1% of the cases respectively. The incidence of vomiting varied significantly with the site of operation for both sexes. The duration of anesthesia was not important in relation to postoperative nausea and vomiting, but there appeared to be an upward trend as duration increased. The gastric tube had a favorable effect, while endotracheal intubation and the use of relaxants had no appreciable influence on vomiting.

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AGRANULOCYTOSIS CAUSED BY PHENOTHIAZINE DERIVATIVES

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Agranulocytosis has sometimes followed the use of chlorpromazine and promazine, and there is reason to assume that it can also be induced by sufficient amounts of other drugs of the phenothiazine group. In most of the known cases this reaction occurred during the first 15 weeks of drug administration. In the cases here described two men, aged 72 and 41 years, had received chlorpromazine and promazine respectively; a third, aged 49, had received both drugs. At the height of the agranulocytosis the first patient had only 2% neutrophils and a total leukocyte count of 900 per cubic millimeter; in the other two patients the neutrophils vanished. Evidence in these cases indicated that the reactions represented individual idiosyncrasies to cumulative doses of the drugs and that fatalities can be prevented by sufficient alertness and prompt recognition of incipient neutropenia. The three patients recovered without signs of residual damage.

That a specific drug reaction could cause granulocytopenia was demonstrated in 1934 by Madison and Squier[1] and confirmed by Sturgis and Isaacs.[2] Both groups showed that small test doses of aminopyrine were the etiological agent in patients recovered from agranulocytic angina. The phenothiazine ring (see figure), containing sulfur and nitrogen, is toxic to bacteria, insects, and helminths; is present in a veterinary vermifuge; and is a constituent of the parent substance of thionine dyes such as methylene blue. In humans, phenothiazine induces hemolytic anemia, toxic hepatitis, skin irritation, and photosensitization. The first derivative which was found to be pharmacologically useful is chlorpromazine, which was introduced in 1952 in France. Its first trade name (Largactil) was designed to indicate its large action and many uses. This drug is similar structurally to promethazine (Phenergan) but lacks antihistaminic properties. At the present time, there are six other derivatives in use which have actions similar to chlorpromazine (see figure). Not included in this list are the most recent drug, trimeprazine (Temaril), which is similar to phenergan and has antihistaminic properties, and the tranquilizers thioridazine (Mellaril) and trifluoperazine (Stelazine). Reports since 1954 indicate that agranulocytosis is a side-effect of chlorpromazine therapy, and this reaction has also been noted with promazine, promethazine, prochlorperazine, perphenazine, and mepazine.

Chlorpromazine

A review of 58 cases from the literature and one case reported here provides the basis for some generalizations on the nature of agranulocytosis associated with chlorpromazine therapy. Reviews[3] provide information on 32 of the cases, and the remainder have been reported singly. The incidence of chlorpromazine agranulocytosis may be as high as three cases in 1,000 patients.[4] Data from 59 cases given in table 1 show the mean and the range. In most cases reported the patients had been given neuropsychiatric diagnoses; use of chlorpromazine in mental health institutions has undoubtedly influenced the reported mean age of 54 years (range

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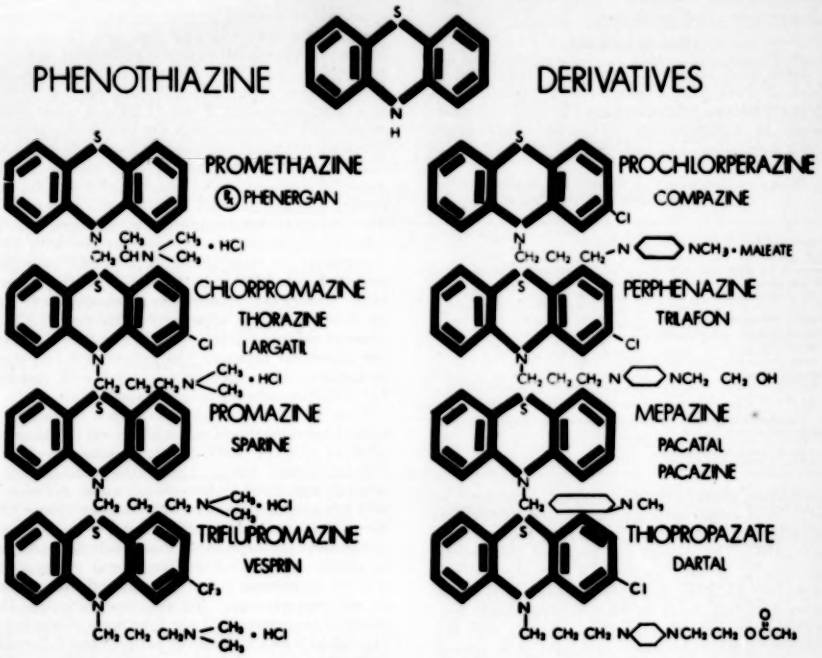
26 to 88 years). A great difference in sensitivity of patients is evidenced by the range of doses (from 1 to 52 Gm. [mean, 12.3]) of total drug administered on consecutive days prior to the reaction. The mean number of days of consecutive administration was 50 (range, 13 to 171), with a standard deviation of 26 days. This would suggest that two-thirds of the reactions can be expected to develop during the first 76 days and 95% during the first 15 weeks of drug administration. No other drug was administered concurrently in 35 cases, and chlorpromazine was the only phenothiazine derivative given in the remainder.

Of the entire group, 31 received hormone therapy in the form of ACTH, prednisone, or cortisone as well as antibiotics. The remainder received antibiotics alone. Steroid therapy did not seem to influence either mortality or recovery time. Twenty-two deaths with agranulocytosis were recorded. In general, about 10 days elapse after development of agranulocytosis and withdrawal of the drug before the leukocyte count returns to normal. The bone marrow "responds" (i. e., begins to recover) at least one week before the leukocyte count becomes normal. The time before return to normal or elevated total leukocyte levels has ranged in various reports from 5 to 16 days.

Promazine

Eleven cases plus one case here have been reported of agranulocytosis associated with promazine therapy.[5] Ages of patients and mean total dose are quite similar to those for chlorpromazine (table 1). From the experience in a few cases, it would appear that 95% of the reactions occur during the first 11 weeks of therapy. Three deaths have been reported, and the results of corticosteroid therapy and the recovery trends are also quite similar to those for chlorpromazine agranulocytosis. Bone marrow changes in cases of agranulocytosis after use of both these drugs are the same. Either there is almost complete absence of granulocytic elements or, if recovery has begun, there is predominance of progranulocytes or myelocytes. Erythropoiesis and thrombopoiesis have usually been reported as



normal, except for approximately 16 cases in which the marrow findings were described as showing pancytopenia.

Other Derivatives

There is insufficient information on agranulocytic reactions to some of the other derivatives to permit any distinctions to be made. Mepazine agranulocytosis in four cases has followed a pattern similar to that of disease after chlorpromazine and promazine. A patient who had recovered from a reaction to chlorpromazine was shown to be sensitive to prochlorperazine and promazine.[36]

Report of Cases

Case 1.—A 72-year-old male was transferred on Sept. 22, 1957, from a mental institution to the Ann Arbor Veterans Administration Hospital with diagnoses of schizophrenia and acute appendicitis. Prior medication had included intermittent use of

Table 1.—*Data from Case Reports of Agranulocytosis Caused by Phenothiazine Derivatives**

	Chlorpromazine	Promazine
Cases reported as of August, 1958, no.†	59	12
Age (mean), yr.	54(26-88)‡	57(46-74)
Mean total dose, Gm.	12.3(3.1-52.5)	14.4(2.8-37.0)
Consecutive days drug was given prior to reaction	58(13-171) S.D.§=26	41(14-83) S.D.=19
Deaths due to agranulocytosis	22	3
Steroid therapy, no. of patients	31	4
Recovered	19	2
Died	12	2
Days for response		
Steroid	10(5-16)	9(3-13)
No steroid	10(7-14)	11(8-13)

* Complete bibliography of all case reports will be supplied by the author on request.
† Includes cases reported in text.
‡ Range given in parentheses.
§ S.D.: standard deviation.

antibiotics, phenobarbital, reserpine, occasional injections of meperidine (Demerol), and intermittent injections of chlorpromazine during July and August, 1957. The patient had received chlorpromazine orally, 50 mg. four times a day intermittently from July 14, 1957, until his admission, for a total dose of 7.8 Gm. (table 2). Normal blood values were reported on July 15. Abdominal rigidity and tenderness in the right lower quadrant were present on admission, with 2 to 3+ pitting edema of both lower extremities. His temperature was 102 F (38.9 C). Blood values on admission were as follows: hemoglobin level, 13.5 Gm. per 100 cc.; hematocrit, 43.5%; leukocytes, 900 per cubic millimeter, with 2% neutrophils, 32% small lymphocytes, 58% large lymphocytes, and 2% plasmacytes; reticulocytes, 1%; and platelets, normal in number. His blood type was A negative, Rh positive. Appendectomy performed on the day of admission revealed a mucocele and atypical hyperplasia of the appendix mucosa without inflammation. Sternal marrow aspiration on Sept. 23 yielded a hypoplastic specimen with no mature granulocytic elements and only an occasional myelocyte. There appeared to be diminished erythropoiesis and number of megakaryocytes.

Inflammation of the pharynx developed, and rales were heard in the lower lung fields; he was treated with erythromycin, 1 million units of penicillin daily, and 1 Gm. of streptomycin daily. The febrile course continued from Sept. 22 through Sept. 30, when there was defervescence. Another sternal marrow examination on Sept. 26 revealed hypocellularity with rare occurrence of metamyelocytes and no over-all increase in myelopoiesis. The hemoglobin level was 12.2 Gm. per 100 cc. and leukocytes were 1,200 per cubic millimeter, with 5% neutrophils plus Türk's irritation cells. On Sept. 30 the leukocyte count was 5,250 and on Oct. 1, the day of defervescence, it was 11,200 per cubic millimeter, with 50% neutrophils. On Oct. 1, an aspirated specimen of sternal marrow was hypercellular, with marked increase in granulopoiesis and predominance of myelocytes. Use of antibiotics was discontinued, and the patient's recovery was uneventful. The leukocyte count continued to rise until Oct. 7, when it was 20,000 per cubic millimeter, with 82% neutrophils. It then gradually declined over the next 10 days to 9,000 to 10,000. Subsequently, the patient underwent transurethral resection of the prostate for benign hypertrophy. He received test doses of chlorpromazine (as shown in table 2) without significant reaction. The patient was last seen in January, 1958, when he was doing well, and his blood values were all within normal limits.

Case 2.—A 41-year-old male with a diagnosis of schizophrenic reaction was transferred to this hospital on Oct. 14, 1957. Physical examination was within normal limits. Laboratory studies were normal, with 6,600 leukocytes per cubic millimeter and a hemoglobin level of 14.4 Gm. per 100 cc. On Nov. 12 it was noted that the patient had leukopenia and neutropenia and was febrile. He had received amobarbital (Amytal) and promazine, 250 mg. four times a day intermittently since Oct. 7, and meprobamate, 400 mg. intermittently. He received promazine, 200 mg. four times a day, from Oct. 15 to Nov. 12. A febrile toxic course followed, with pharyngeal ulceration, cervical adenitis with superficial ulceration, and severe sore throat with dysphagia. The lips and tongue were swollen, and the neck had the wooden-hard character of Ludwig's angina. His temperature ranged between 102.0 and 104.4 F (38.9 to 40.2 C). Treatment was with procaine penicillin, 600,000 units; streptomycin, 0.5 Gm., alternating with dihydrostreptomycin; benzathine penicillin G, 600,000 units by mouth; and oxytetracycline (Terramycin), 0.5 Gm. by mouth —all given every six hours.

Sternal aspirate on Nov. 12 was hypocellular, with no evidence of granulopoiesis and decreased numbers of erythropoietic elements and megakaryocytes.

Hemoglobin level was 10.8 Gm. per 100 cc. and hematocrit, 34%. The leukocyte count was 950 per cubic millimeter, with Türk's irritation cells and no neutrophils. The spleen was palpable, and there was a positive urine test for porphobilinogen (negative in a 1:10 dilution). This test was positive on Oct. 29, Oct. 30, and Nov. 1 but was not positive again on repeat determinations, including those at the time of test doses. On Nov. 15 the bone marrow was hypocellular, with normal erythropoiesis and thrombopoiesis. On Nov. 19 the bone marrow was more cellular, with progranulocytes and myelocytes, and the erythroid-myeloid ratio was 1:1. On Nov. 21 there was the first indication of granulopoietic response; leukocytes were 2,700 per cubic millimeter and the temperature abruptly became normal. On Nov. 22, the sternal marrow aspirate was very hypercellular, with increase in granulopoiesis. The leukocyte count continued to rise to a peak of 35,000 per cubic millimeter on Nov. 26, with

Case 3.—A 49-year-old male was admitted to the Neuropsychiatric Institute on May 25, 1957, because of a diagnosis of schizophrenic reaction. Two years previously he had had an episode of jaundice after chlorpromazine therapy. The leukocyte count was 5,700 per cubic millimeter and the hemoglobin level, 14.9 Gm. per 100 cc. Promazine, 50 mg. four times a day, was administered on admission and the dosage was increased gradually to 250 mg. four times a day. A total of 10.3 Gm. of promazine was given over a period of 18 days. Other drugs given included methylphenidate (Ritalin), digitalis, and mercaptomerin (Thiomerin). The patient was transferred to the medical service on the 18th hospital day with a tentative diagnosis of impending thyroid storm, temperature of 102 F, and tachycardia.

At the time of transfer, there were 1,300 leukocytes per cubic millimeter, without neutrophils. Sternal marrow aspiration revealed normal mega-

Table 2.—*Observations in Two Cases at Onset of Therapy, During Agranulocytosis and Recovery, and During Drug Readministration*

	Onset of Therapy	After Stopping Therapy				During Drug Readministration			
Case 1—Chlorpromazine Agranulocytosis									
Date	7/15/57	9/23	9/26	9/30	10/7	11/5	11/20	12/13	
Fever	0	+	+	+	0	0	0	0	
WBC	7,400	900	1,200	5,250	20,000	11,900	9,100	8,350	
Neutrophils, %	45	2	5	51	82	63	70	57	
Hematocrit, %	46	48	41	44	44	36	35	38	
Dose, Gm.	Daily 0.2	Total 7.8	0	0	0	0.025	0.050	0.300	
Case 2—Promazine Agranulocytosis									
Date	10/15/57	11/12	11/20	11/26		12/13	12/16	2/23/58	2/27
Fever	0	+	+	0		0	0	0	0
WBC	6,600	950	1,000	35,000		7,800	7,300	10,000	6,750
Neutrophils, %	80	0	0	88		64	65	77	74
Hematocrit, %	43	34	35	42		43	44	47	46
Dose, Gm.	Daily 0.8	Total 23.2	0	0		0.025	0.050	0	0.3

10% myelocytes, 22% metamyelocytes, and 29% nonsegmented and 25% mature neutrophils; increased platelets; and 1.5 to 2% reticulocytes. The hematocrit was 42%. Serum protein values and liver function test results were all normal.

During the toxic course, the ulcerating lesions did not show evidence of pus formation but cleared up promptly after Nov. 21. The spleen regressed. The patient was later given a week's course of meprobamate, 400 mg. daily, without reaction and was given test doses of promazine without significant reaction (table 2), except that after the 50-mg. test dose he developed a slight rash over his forehead. He received 25 mg. of promazine on Dec. 13 and 50 mg. on Dec. 16, with slight increase in temperature to 99.2 F (37.3 C) and no change in any blood value except for the fact that the percentage of eosinophils increased to 13. The patient was readmitted to the hospital in February, 1958, at which time he received further test doses of the drug without reaction (table 2).

karyocytes, no evidence of granulopoiesis, normoblastic erythropoiesis, and numerous plasmacytes. Use of promazine was discontinued, and antibiotic therapy with penicillin, streptomycin, nystatin (Mycostatin), and novobiocin was instituted. Hydrocortisone therapy was started on June 18 in a dosage of 200 mg. per day. The patient remained febrile (temperature from 99 to 105.6 F [37.2 to 40.8 C]) until June 23, when his temperature became normal. During this acute episode he became jaundiced. The total bilirubin level reached a peak of 11.2 mg. per 100 cc. (5.6 mg. direct) on June 18, 1957, and cleared rapidly thereafter. The leukocyte count on June 25 was 22,600 per cubic millimeter, with 82% granulocytes, including immature forms. Repeat marrow aspiration, done on June 26, showed a striking increase in granulocytic elements, with an erythroid-myeloid ratio of 1:9, all stages of granulocytic development, and a relative increase in myelocytes. The subsequent course of this patient was complicated by the development of an abscess of the forearm and of empyema with bron-

chopleural fistula. Coagulase-positive hemolytic Staphylococcus aureus was cultured from both of these infectious processes. The infections cleared after surgical drainage. The hemoglobin level on Sept. 6 was 10.3 Gm. per 100 cc., and leukocytes were 5,000 per cubic millimeter.

Comment

The mechanism of agranulocytosis produced by phenothiazine-derivative drugs appears to follow a definite pattern. In a patient* who had developed a reaction to chlorpromazine, the drug was readministered at 10-mg. and 25-mg. doses without effect, and the blood reaction was then reproduced after 1.3 Gm. given over a 13-day period. Small doses will not reproduce a reaction.[7] Table 2 demonstrates the course of the agranulocytosis in two of our patients and negative results by readministration of small amounts of the drug. This is not the type of result which one would expect if a highly sensitive immunological mechanism were responsible, as is the case with reactions to aminopyrine. Attempts have been made to demonstrate leukoagglutinins in phenothiazine agranulocytosis* without success. In case 2, leukoagglutinins were sought by adding the patient's serum taken during the height of the agranulocytic action to normal leukocytes in the presence of a small amount of promazine. No leukoagglutination over that of the mixture of normal serum and normal leukocytes could be demonstrated. It would appear that this type of reaction is a drug idiosyncrasy or cumulative toxicity in which large doses of the drug given consecutively over a period of days produce bone marrow depression which is initially manifested in the granulocytic series. This reaction can be reproduced in the same person by giving a comparable dose of the drug again. It may be that agranulocytosis would recur if phenothiazine derivatives were given to a person who had developed a reaction after administration of one of these compounds. These drugs should probably be classified as agents occasionally associated with the occurrence of granulocytopenia, as suggested by Wintrobe and Cartwright.[9] It is interesting to note that jaundice and agranulocytosis do not very often appear concurrently.

The efficacy of steroid therapy in this form of agranulocytosis is debatable. The usefulness of corticotropin and cortisone in some blood disorders, especially those associated with continuing immune reactions, is well recognized.[10] However, the beneficial effects of these hormones in drug-induced agranulocytosis appear not to be well established. Adrenal cortex stimulation induces eosinopenia and neutrophil leukocytosis and evidence of erythrocytic proliferations. This is not constant or prolonged, except for the eosinopenia; the values revert to normal after use of adrenal cortical hormones is stopped.[11] A review of case reports suggesting beneficial effects of steroid therapy reveals that, after the recognition of the leukopenia and stopping of the use of the drug, evidence of bone marrow response appeared after 7 to 10 days, which is the same time range as that for those patients who did not receive steroids. The same pattern has been noted in case reports of agranulocytic reactions to drugs other than phenothiazine derivatives. The question has been raised[12] as to whether corticosteroid therapy is indicated. It may be argued that adequate antibiotic coverage and supportive care during a period of agranulocytosis should be sufficient therapy and that the administration of steroids might suppress a much needed immune response. The tabulation in table 1 of deaths due to agranulocytosis after the use of phenothiazine derivatives affords no argument either for or against the use of steroids. Experimental observations would indicate that steroids do not have a beneficial effect on the bone marrow after myeloid depression. It was noted in animals that after irradiation[13] the administration of cortisone had an adverse effect on bone marrow regeneration. It has been reported[14] that the leukopenia induced by nitrogen mustard administration can be increased by cortisone.

Splenomegaly was noted in case 2 and in several of the cases previously reported. The enlargement occurred during the period of agranulocytosis and disappeared on recovery. Splenomegaly may represent a reticuloendothelial and lymphoid reactive hyperplasia during the period of agranulocytosis.

Summary and Conclusions

The phenothiazine derivatives in general use at the present time include chlorpromazine, promazine, mepazine, promethazine, prochlorperazine, perphenazine, triflupromazine, thiopropazate, and trimeprazine. Agranulocytosis appears to be a definitely established reaction to chlorpromazine and promazine, and there are indications that other phenothiazine derivatives may have this potential action.

Most of the reactions appear to occur within the first 15 weeks of consecutive administration. If the agranulocytosis is recognized promptly, patients recover completely, usually about 10 days after use of the drug is stopped. Antibiotics, but probably not corticosteroids, should be administered.

The reaction appears to be an individual idiosyncrasy to a cumulative toxic dose of the drug. Cross sensitivity to other phenothiazine derivatives appears to be likely in the case of persons who have had agranulocytosis after the administration of one of these compounds. Readministration of small test doses does not result in a reaction, and leukoagglutinins have not been demonstrated.

Awareness and recognition of this drug reaction and familiarity with the various phenothiazine derivatives should prevent fatal reactions from de-

veloping in the future. Recovery appears to be complete and without residual bone marrow abnormality.

Dr. R. C. Bishop, University of Michigan Medical Center, provided the data and observations in case 3.

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CLINICAL NOTES

SULFHEMOGLOBINEMIA DUE TO ACETOPHENETIDIN

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The observation of cyanosis in a patient without findings of respiratory or cardiovascular disease or polycythemia vera leads one to consider as its cause the presence of an altered hemoglobin.[1] Although 5.0 Gm. of reduced hemoglobin is usually necessary to produce cyanosis, only 1.5 Gm. of methemoglobin or 0.5 Gm. of sulfmethemoglobin will cause detectable cyanosis.[2]

Once sulfhemoglobinemia or methemoglobinemia is suspected, spectrometric examination of the blood will confirm this diagnosis. However, at this point the sometimes difficult task of finding the offending agent begins, for numerous drugs have been incriminated, the most common of which are nitrates, sulfonamides, and aniline derivatives.[3] The following case history is illustrative of this problem.

From the Division of Laboratories (Drs. Polesky and Sacks) and the Department of Medicine (Dr. Thorner), Cedars of Lebanon Hospital.

Report of a Case

A 37-year-old woman, an interior decorator, was admitted to the hospital for the third time with a complaint of recurrent spells of weakness. For the past several years she had had spells of weakness which recently became more pronounced and were associated with increasing fatigue and lethargy. A few months prior to this admission she had completed a full-term pregnancy complicated only by low back pain. During the two months preceding her hospitalization, she had recurrent nonspecific low back pain. For relief she took up to 10 tablets daily of Daprisal and about 10 tablets daily of either Empirin compound or Bufferin. No history of ingestion of any other drugs was elicited. She was not exposed to heavy metals, other than paints. The family history and her own history were noncontributory. Review of systems revealed no cardiorespiratory or gastrointestinal symptoms.

Examination revealed an extremely lethargic, well-developed, well-nourished young woman. Her skin, lips, and nailbeds were a peculiar ashen-gray color. Her pulse rate was 66 per minute, respirations 20 per minute, blood pressure 110/60 mm. Hg, and temperature 98.6 F (37 C). The chest was clear. There was no cardiac enlargement or murmurs. The liver and spleen were not palpable. Edema was absent. Reflexes were equal and active, and no sensory loss or muscle weakness was detected. Psychiatric evaluation revealed a subsiding reactive depression.

Laboratory findings showed a hemoglobin level of 12.3 Gm.%; hematocrit value 39%; mean corpuscular hemoglobin concentration 32%; white blood cell count 6,250 per cubic millimeter, with 75% neutrophils (74% polymorphonuclear cells, 1% stab forms), 23% lymphocytes, 2% monocytes; platelets adequate; red blood cell morphology unremarkable; sulfmethemoglobin 0.8 Gm.%; methemoglobin absent. Results of urinalysis were negative; urine coproporphyrin, trace, and no uroporphyrin or porphobilinogen. X-rays of the chest, skull, and wrists were not remarkable. An electrocardiogram showed inverted T waves in leads aVR and aVL and V_1, a deep Q wave in aVL, and a low R wave in V_1 to V_6.

The patient's course was uneventful and afebrile. All drug therapy was stopped. Five cubic centimeters of 1% methylene blue given intravenously had no effect on the cyanosis. Her depression lifted, and she was discharged with decreasing cyanosis. In six weeks the cyanosis had disappeared completely.

Comment

The identification of the altered hemoglobin level is relatively easy and is of importance in deciding the form of therapy to be undertaken.[1] The level of sulfmethemoglobin (0.8 Gm.%) was found by analysis to exceed the minimum level (0.5 Gm.%) necessary for the production of cyanosis.

Although the exact chemical nature of sulfmethemoglobin is unknown, it is thought that an atom of sulfur is introduced into the hemoglobin molecule and that there is a change in the globin linkage with heme.[2] This compound has a characteristic absorption band at 618μ. Methemoglobin has a band at 630μ. Sulfmethemoglobin has a brownish color which, unlike the brownish color of methemoglobin, does not become red on standing or after bubbling oxygen through it. Further, the absorption band of methemoglobin disappears after the addition of a few drops of 5% potassium cyanide to the solution.[2]

It is felt that the etiological agent responsible for the ashen-gray cyanosis in this case was the acetophenetidin present in the drugs that the patient had ingested for relief of her "arthritic pains." Daprisal contains 0.16 Gm. of acetophenetidin, 0.16 Gm. of acetylsalicylic acid, 0.032 Gm. of amobarbital, and 0.005 Gm. of dextro amphetamine sulfate; Empirin compound contains 0.16 Gm. of acetophenetidin, 0.23 Gm. of acetylsalicylic acid, and 0.03 Gm. of caffeine; and Bufferin contains 0.325 Gm. of acetylsalicylic acid, 0.05 Gm. of aluminum glycinate, and 0.10 Gm. of magnesium carbonate but no acetophenetidin. This patient had a daily intake of up to 3.2 Gm. of acetophenetidin over a two-month period, or a total intake of about 192 Gm. of acetophenetidin.

In previous reports the acetanilid in Bromoseltzer and other preparations was the etiological agent most commonly incriminated.[3] In 11 cases in the recent literature, the acetophenetidin contained in proprietary drugs has been implicated as the cause of sulfhemoglobinemia.[1]

Both acetophenetidin and acetanilid have similar metabolic pathways.[3a] When given with sulfur, these drugs produce sulfhemoglobinemia in rabbits and dogs.[3] Frequently, in cases of cyanosis secondary to sulfhemoglobinemia, the patients are constipated, and it is postulated that a source of sulfur from the intestine is partially responsible. The rare case of enterogenous sulfhemoglobinemia is thought to be caused by such a mechanism. In our patient there was no constipation, nor were sulfur-containing drugs being administered.

The presence of anemia in patients with sulfhemoglobinemia is inconstant.[3] In most of the previously reported cases, anemia was not a feature or, if present, was secondary to some other factor. Careful studies have shown that once sulfmethemoglobin is in a cell it remains there for the life of that cell. The life span of these cells is normal.[3] Neither methemoglobin nor sulfmethemoglobin is a toxic substance; they produce toxic symptoms by causing anoxia that results from the reduced oxygen capacity of hemoglobin so altered.[2]

While intravenously given methylene blue abolishes acquired methemoglobinemia, there is no satisfactory therapy for sulfhemoglobinemia except withdrawal of the offending drug.

Summary

A case of sulfhemoglobinemia with cyanosis was caused by acetophenetidin. Physicians should be alerted to the dangers of this agent, which is present in many proprietary drugs used by the general public and the profession.

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HYPOKALEMIC MUSCLE PARALYSIS ASSOCIATED WITH ADMINISTRATION OF CHLOROTHIAZIDE

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Chlorothiazide is a new orally given diuretic whose potency equals that of the parenterally given mercurial diuretics.[1] While in vitro it appears to be a carbonic anhydrase inhibitor, the latter effect is not strikingly evident in vivo.[2] It acts directly on the renal tubules [3] in a manner similar to that of the mercurial diuretics.[4] The result is an increased excretion of sodium, potassium, and chloride in the urine, accompanied by diuresis.

The side-effects do not appear to be troublesome.[5] Among those reported are (1) gastrointestinal disturbances, including nausea, vomiting, abdominal cramps, and epigastric distress; (2) hemorrhagic manifestations in which patients exhibited hematuria and petechiae without changes in the clotting mechanism; and (3) an exaggeration of epilepsy due to systemic alkalosis.[5a] Wilkins [5b] has reported sexual impotence as a complication of chlorothiazide therapy and Drerup and co-workers [6] treated a patient who developed jaundice with pathological evidence of bile stasis while receiving the medicament. Transient skin rashes have also been reported,[5] as have hyperglycemia and glycosuria.[1] A clinical picture of impending hepatic coma [7] and ammonia intoxication [8] in patients with liver disease who were treated with chlorothiazide has also been observed.

Hypokalemia is the most important side-effect.[5] It is noted in 40% of patients receiving chlorothiazide without supplemental potassium.[1] In half of these cases the serum potassium level falls below 3.5 mEq. per liter [5b] and may be accompanied by weakness and trembling. Caution has been urged in the use of chlorothiazide in patients with renal [5c] and cardiac disease.[10] Lowering of the serum potassium level predisposes patients with heart disease to cardiac arrhythmias and digitalis toxicity.[5c] This is particularly liable to occur if such patients are placed on a low-sodium diet, for in this situation there is an increased excretion of potassium by the kidney due to the unavailability of sodium.

A patient who was recently treated with chlorothiazide developed a marked hypokalemia accompanied by selective muscle paralysis. The latter responded dramatically to the administration of potassium. Dr. Gibson, director of medical research of Merck Sharp & Dohme, stated that according to the information available to him this case is the first instance in which the serum potassium level had dropped so low and muscle paralysis occurred while chlorothiazide was being administered.[11] The unusualness of this case merits its publication.

Report of a Case

A 60-year-old man was referred for medical evaluation because his ophthalmologist told him that there were "signs of high blood pressure in the eyes." When first seen on Dec. 4, 1958, he had no other complaints. His history was noncontributory, including no personal or familial episodes of periodic paralysis. Findings of the initial physical examination were within normal limits except for overweight (height 5 ft. 7 in. [170.2 cm.], weight 201 lb. [91.2 kg.]) and hypertension (blood pressure 180/124 mm. Hg). Funduscopic examination revealed some arteriolar constriction. Hemoglobin concentration was 12.5 Gm.%. Urinalysis revealed a specific gravity of 1.010; no albumin or sugar was present; and microscopic examination showed an occasional red blood cell and white blood cell per high-power field. Therapy at that time consisted of a 1,200 calorie diet and 250 mg. of chlorothiazide to be taken twice daily. The patient was instructed to return in two weeks.

On Dec. 19 when he was seen again he stated that he felt well but that he had not followed the diet. His weight at that time was 212 lb. (96.1 kg.)

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and blood pressure 190/80 mm. Hg. The patient was again advised about the necessity of following a low-calorie diet, and because the systolic pressure was still moderately elevated the chlorothiazide dosage was increased to 500 mg. twice daily.

During two subsequent visits on Dec. 29, 1958, and Feb. 6, 1959, his weights were 205 and 206 lb. (93.0 and 93.4 kg.). The blood pressure recordings were 170/95 and 165/90 mm. Hg. He felt well and stated that following the diet consisted in avoiding starchy foods. The chlorothiazide therapy was continued and dextro amphetamine was added at the last visit to aid him in curbing his appetite.

On March 2 he was seen at home because for the past two days he had been unable to bend his left thigh and raise his right arm. He added that one week prior to the onset of these symptoms he had noted a similar weakness in his right lower extremity. This lasted for two days and then cleared spontaneously. He had continued to take the chlorothiazide up to the time of examination. Physical examination revealed a complete inability on the part of the patient to flex his left thigh and to abduct his right arm. There were no sensory disturbances and the reflexes were normal. No pathological reflexes could be elicited and there was no weakness of any other muscle group. There was no elevation of the temperature or nuchal rigidity.

The patient was immediately hospitalized at University Hospital, where results of an initial complete blood cell count and urinalysis were essentially normal. A spinal tap done on admission (with difficulty) revealed an initial pressure of 270 mm. H_2O. The fluid was clear and contained nine white blood cells per cubic millimeter. Result of the Pandy test was slightly positive, and that of the Kolmer test was negative. Results of trichinosis complement-fixation and flocculation tests of the serum were negative. Neutralization studies on stool and cerebrospinal fluid specimens were negative for poliomyelitis, Coxsackie, and enteric cytopathogenic human orphan (ECHO) viruses.

Serum potassium level determined on the day of admission was 1.65 mEq. per liter. Because of the exceptionally low level the determination was repeated the following day and an identical result was obtained. It was then felt that the hypokalemia was secondary to the administration of chlorothiazide and was also responsible for the patient's symptoms. An electrocardiogram done at that time showed widening of the QRS complex with depressed S-T segments, and widened, inverted T waves fusing with prominent, upright U waves—all compatible with hypokalemia. On March 3 an intravenous infusion of 40 mEq. of potassium chloride was given, and immediately afterward the serum potassium level was 2.15 mEq. per liter. At this time the patient stated that the involved extremities felt somewhat stronger. However, a clinical examination failed to demonstrate any change. The patient was given 2 Gm. of potassium chloride by mouth that evening. The next morning the serum potassium level was 2.8 mEq. per liter and his general condition was unchanged. He was then started on therapy with potassium chloride, 2 Gm. four times daily. The morning of March 5 he awoke with full use of the affected extremities. His serum potassium level at that time was 2.95 mEq. per liter. The next day the potassium chloride dosage was reduced to 6 Gm. daily and was continued until March 10.

Serum Electrolyte Studies and Potassium Chloride Administration

	March										April
Serum Electrolytes, mEq. Liter	2	3	4	5*	6	7	8	9	10	11	3
Potassium	1.65	1.65† 2.15‡	2.8	2.95	3.6	3.9		5.05	5.1	5.5	4.8
Sodium				151.0 (repeated)		141.0		141.0	137.0	135.0	136.0
Chloride						102.0		106.0	109.5		109.0
HCO_3						27.7		25.6			
Potassium chloride administration		40 mEq. I.V. + 2 Gm. orally	2 Gm. q.i.d.	2 Gm. q.i.d.	2 Gm. t.i.d.	2 Gm. t.i.d.	2 Gm. t.i.d.	2 Gm. t.i.d.			

* Muscle paralysis no longer present.
† Before I.V. administration of potassium chloride.
‡ After I.V. administration of potassium chloride.

On March 5 the patient's serum sodium level was found to be elevated (see table) on successive determinations. Because of the possibility that aldosteronism might be present the salivary potassium level, which is characteristically elevated in this condition,[12] was determined on March 10 and found to be 21 mEq. per liter, which appeared to be within normal limits.[13] These tests, subsequent electrolyte studies, and the lack of resistance to therapy ruled out the diagnosis of aldosteronism. The patient was discharged from the hospital on March 11, feeling perfectly well. He was seen in April, at which time there was no evidence of recurrence of muscle paralysis, and his serum electrolyte levels were normal.

Summary and Conclusions

A patient developed muscle paralysis subsequent to hypokalemia during the administration of chlorothiazide. The marked drop in the serum potassium level and the clinical symptomatology were unusual; this appears to be the first such case reported.

The elevation of the serum sodium level accompanying this marked decrease in serum potassium is a change similar to that seen in aldosteronism. Perhaps, as has been previously suggested,[1] chlorothiazide in some way exerts its pharmacological action through the activation of aldosterone.

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HEPATIC DAMAGE DURING CHLORPROPAMIDE THERAPY

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Recently a new arylsulfonylurea, chlorpropamide (Diabinese), has been released for the management of diabetes mellitus. Its mode of action is similar to that of other sulfonylureas, but it has a more potent hypoglycemic effect than tolbutamide and is excreted more slowly. As a result, lower dosages may be used and a fairly constant blood level obtained. Studies of acute and chronic conditions in animals have shown that this drug possesses a low order of toxicity.[1] Clinical trial in approximately 2,000 cases, for periods up to one year, indicates that in some patients hepatic function tests may show transient deviations from the normal. In general these abnormalities have not been indicative of serious hepatic dysfunction and have reverted to normal even when the drug therapy was not discontinued. In eight cases jaundice appeared, sometimes associated with a skin rash and eosinophilia. These cases have all occurred within two to five weeks of beginning therapy and have been characterized by an elevation of the alkaline phosphatase level and by the presence of intracanalicular biliary stasis. When chlorpropamide therapy was discontinued, the jaundice disappeared and the liver reverted to normal.[1a] It is the purpose of this communication to report three additional cases of liver injury which occurred in a series of 49 patients treated with chlorpropamide in a clinical trial of the drug at the diabetes clinic of the Bronx Hospital.

From the Diabetes Clinic and the Department of Medicine of the Bronx Hospital.

Report of Cases

Case 1.—A 50-year-old woman had been known to have diabetes for 20 years. Her condition had been managed by diet and administration of 100 units of globin zinc insulin daily. In an effort to improve the degree and stability of her control, she was given in addition 1 Gm. of chlorpropamide per day. About three weeks later, she noted sensations of chill, weakness, and loss of appetite, followed in a few days by the discovery of dark urine, light stools, and rash on her trunk. With the passage of an additional week, by which time she had ingested a total of 27 Gm. of chlorpropamide, she noted jaundice. There was no pain, fever, nausea, or vomiting. Her history was negative for liver

or biliary tract disease. Her alkaline phosphatase level, which had been 10 King-Armstrong units before the drug therapy was started and 11 King-Armstrong units after two weeks of therapy, was found to be 37 King-Armstrong units. The white blood cell count was 6,300 per cubic millimeter, with a differential of 59% segmented forms, 30% lymphocytes, 2% monocytes, and 9% eosinophils. She was hospitalized on Oct. 10, 1958, for further studies.

The findings of the physical examination were negative, except for the presence of jaundice, a diffuse macular eruption on the trunk, and a soft, tender liver edge 2 fingerbreadths below the costal margin. Laboratory data on admission included the following findings: the alkaline phosphatase level was 80 King-Armstrong units, the serum bilirubin level 8.9 mg.%, and the cholesterol level 630 mg.%, with 34% esters. The thymol turbidity was 1.6 units and the cephalin flocculation test negative. The hemoglobin level was 11.6 Gm.%, and the white blood cell count 7,600 per cubic millimeter, with 74% segmented forms, 20% lymphocytes, and 6% eosinophils. Platelets numbered 490,000 per cubic millimeter. Results of urinalysis were negative, except for the presence of bile. On Oct. 16, the serum bilirubin level reached a peak of 9.4 mg.%, the alkaline phosphatase level was 86 King-Armstrong units, and the serum cholesterol level 770 mg.%. By the time of the patient's discharge these values had fallen to a serum bilirubin level of 0.8 mg.%, an alkaline phosphatase level of 26 King-Armstrong units, and a serum cholesterol level of 262 mg.%, with 75% esters respectively. The cephalin flocculation and thymol turbidity remained normal. On two occasions the serum albumin level was 4.1 and 4.0 Gm.%, respectively, and that of serum globulin 2.6 and 2.3 Gm.% respectively. A needle biopsy of the liver, performed on Oct. 16, showed normal liver architecture. There was mild pigmentation of the Kupffer cells and slight capillary bile stasis. While a spotty inflammatory reaction in the portal tracts was noted, no inflammatory or degenerative changes were observed in the hepatic cells. A gallbladder series performed on Nov. 10 showed several negative shadows suggestive of gallstones. The patient remained afebrile throughout her hospital stay. The rash and eosinophilia cleared by the fifth hospital day. Her diabetes was controlled by means of a diet containing 150 Gm. of carbohydrates, 75 Gm. of proteins, and 80 Gm. of fats, and the administration of 80 units of NPH insulin daily. She was discharged on Nov. 14, 1958, and was still asymptomatic when seen for a follow-up examination in January, 1959.

Case 2.—A 67-year-old woman was referred on Nov. 5, 1958, for admission from the diabetes clinic of the Bronx Hospital because of a rise of her alkaline phosphatase level from 13 to 53 King-Armstrong units while on chlorpropamide therapy. The patient had been a known diabetic for one year and had not followed a prescribed diet or taken insulin. Six weeks prior to her admission to the diabetes clinic, on Sept. 26, she appeared at the outpatient department of the Bronx Hospital complaining of marked polyuria and polydipsia, with weakness. On that day therapy with chlorpropamide, 1 Gm. per day, was started, and she was placed on a 1,500-calorie diet. The alkaline phosphatase level, which was 13 King-Armstrong units on Oct. 15 (three weeks after the onset of treatment), rose to 53 King-Armstrong units on Oct. 29 (five weeks after the onset of treatment). She experienced no pain, nausea, or anorexia. Her history was negative for liver or biliary tract disease. Medication was discontinued on Oct. 29, after a total of 32 Gm. of chlorpropamide had been taken.

At the time of admission, Nov. 5, 1958, she appeared asymptomatic, afebrile, and comfortable. There was no jaundice. The only significant finding was a soft, nontender liver, palpable 1 fingerbreadth below the costal margin. The remainder of the findings of the physical examination were normal.

The patient was put on a 1,500-calorie diet without insulin therapy. On admission the hemoglobin level was 79% (Sahli method) or 11.4 Gm.%; the red blood cell count was 4,200,000 per cubic millimeter; the total leukocyte count was 9,000 per cubic millimeter, with a differential of 1% eosinophils, 61% segmented forms, 37% lymphocytes, and 1% monocytes; and platelets numbered 215,000 per cubic millimeter. A sulfobromophthalein test on Nov. 5 showed 14% retention at the end of 45 minutes. The prothrombin time was 88% of control on the same day. On Nov. 6, the second hospital day, the blood glucose level was 153 mg.%, the van den Bergh reaction negative, the serum bilirubin level 0.2 mg.%, and the urea nitrogen level 14 mg.%. The total serum protein level was 6.7 Gm.%, with an albumin level of 4.5 Gm.% and a globulin level of 2.2 Gm.%. The alkaline phosphatase level was 22 King-Armstrong units. The total cholesterol level was 304 mg.%, with 72 mg.% of the total as esters. The prothrombin time was 42% of control (Smith's method). The thymol turbidity was 0.7 units and cephalin flocculation was negative at the end of 24 and 48 hours respectively. The urine did not contain bile. A needle liver biopsy performed on Nov. 11 showed no abnormality of architecture. A fair number of hepatic cells showed hydropic nuclei and some showed hyperchromatic nuclei. The portal tracts were mildly infiltrated with round cells. There was no evidence of bile stasis. On Nov. 14 the alkaline phosphatase level was 18 King-Armstrong units, the serum bilirubin level 0.4 mg.%, and the sulfobromophthalein test showed 5% retention at the end of 45 minutes. A gallbladder series performed on Nov. 19 gave normal results. On Nov. 20, the alkaline phosphatase level

was 15 King-Armstrong units, and the total cholesterol level was 211 mg.%. The patient remained asymptomatic throughout her hospital stay and was discharged on Nov. 25, 1958, with her condition well controlled by administration of 20 units of NPH insulin daily. At a follow-up examination in January, 1959, she was asymptomatic and appeared clinically well.

CASE 3.—A 57-year-old housewife had been known to have diabetes for nine years. The disease had been well controlled by diet and administration of NPH insulin 90 to 110 units daily. She was admitted to the Bronx Hospital on Nov. 10, 1958. On Oct. 10, one month prior to her admission, therapy with chlorpropamide, 0.5 Gm. per day, had been started, and the NPH insulin intake was reduced gradually to 70 units daily. On Oct. 25, two weeks after the onset of treatment, the patient noted malaise, vague abdominal pains, and epigastric discomfort. On Nov. 7, two weeks later and three days prior to admission, she noted a skin eruption, light stools, and dark urine. There was no pain, nausea, or vomiting, but mild anorexia was noted. Her history was negative for liver or biliary tract disease. She discontinued the chlorpropamide therapy, but continued to take 70 units of NPH insulin daily. The total amount of chlorpropamide taken was 12.5 Gm. On Nov. 10, jaundice appeared and she was hospitalized. Her alkaline phosphatase level, which had been 13 King-Armstrong units on Oct. 16, one week after the onset of treatment with chlorpropamide, had risen to 17 King-Armstrong units on Nov. 5.

Physical examination revealed a middle-aged, well-nourished, well-developed female, afebrile and in no distress. There was jaundice of the sclerae, skin, and mucus membranes. A soft, nontender liver was palpable 1 fingerbreadth under the costal margin, and a scanty macular pink rash was noted on the chest. The remainder of the findings of the physical examination were normal. The patient was kept on a diabetic diet of 1,500 calories and received 70 units of NPH insulin daily. No other medication was given. The blood chemistry on Nov. 11 revealed a glucose level of 211 mg.% and a urea nitrogen level of 16 mg.%. The prothrombin time was 100% of control (Smith's method). The erythrocyte sedimentation rate was 79 mm. at the end of one hour (Westergren). On the same day, the hemoglobin level was 78% (Sahli method) or 11.3 Gm.%, the total number of leukocytes 7,050 per cubic millimeter, with a differential count of 3% eosinophils, 53% segmented forms, 43% lymphocytes, and 1% monocytes. The results of urinalysis were negative, except for a trace of bile. Urobilinogen was present in a 1:1 dilution. On Nov. 14 the blood showed an alkaline phosphatase level of 78 King-Armstrong units, the van den Bergh reaction was direct, delayed, with a serum bilirubin level of 1.4 mg.%. The total serum protein level was 6.8 Gm.%, with the albumin level 4.1 Gm. and the globulin level 2.7 Gm. The total cholesterol level was 432 mg.%. Cephalin flocculation was negative in 24 and 48 hours, respectively, and thymol turbidity 1.5 units. The blood glucose level was 168 mg.%. By Nov. 14 the rash was no longer discernible and the jaundice barely perceptible. A needle liver biopsy performed on the second hospital day was reported as showing normal hepatic architecture, with intense infiltration of the portal tracts by acutely and chronically inflamed cells. Mild bile stasis was noted, as well as some vacuolization of a number of liver cells. On Nov. 18 the serum bilirubin level was 1.1 mg.% and the alkaline phosphatase level was 43 King-Armstrong units. The gallbladder series done on Nov. 19 showed no pathology. The patient signed out against advice on Nov. 20, 1958, and did not appear for a follow-up examination.

Comment

The benign course of the hepatic damage, the elevated alkaline phosphatase values, and the liver biopsies demonstrating bile stasis make the type of jaundice due to chlorpropamide therapy similar to that due to thorazine hydrochloride [2] or to methyl testosterone.[3] This variety of hepatic damage, which may or may not be accompanied by jaundice, is characterized by intracanalicular obstruction due to edema and cellular infiltration around the minute intrahepatic bile ducts. It is to be noted that the pathological findings revealed by liver biopsy may be minimal even with fairly high elevations of the levels of serum alkaline phosphatase or bilirubin. The latent period before the onset of jaundice (or rising alkaline phosphatase levels) and, in two of our cases, the prodromal symptoms and the accompanying rash and eosinophilia, suggest that hypersensitivity may be the mechanism involved. As in the case of thorazine hepatitis, this sensitivity apparently may disappear, since the drug therapy may be resumed at a later date without a recurrence of the untoward hepatic effects. This was not tried in any of our cases, but has been done many times with thorazine [4] and by Hamff and co-workers [5] with chlorpropamide without repetition of the jaundice.

In order to detect this type of reaction to chlorpropamide, the serum alkaline phosphatase level should be determined at weekly intervals at least during the first six weeks of its administration and use of the drug discontinued if the value rises above normal. In our experience to date, these cases have all occurred within one to six weeks after onset of therapy, and the jaundice is generally preceded by a rash. According to Shay and Siplet,[6] a rise in the level of serum alkaline phosphatase indicates hepatic sensitivity, which may be reversed by discontinuation of the drug therapy. Discontinuation of use of the drug was the only treatment employed in the cases presented. It is to be noted that the dosages employed in these

cases, 0.5 to 1.0 Gm. daily, were larger than those currently being recommended by the manufacturer. Because of the slow excretion rate of chlorpropamide, initial dosage should be 0.25 to 0.5 Gm. daily. In occasional cases as little as 100 mg. daily can be used as a maintenance dosage.

Summary and Conclusions

Hepatic demage occurred in 3 out of 49 patients employed in a clinical trial of chlorpropamide (Diabinese) therapy. The jaundice which occurred in two of the three cases was demonstrated to be due to intracanalicular bile stasis. This could not be shown in the third case, where a sharp rise in the alkaline phosphatase level occurred without jaundice; but the elevation in the alkaline phosphatase level and the abnormal retention of sulfobromophthalein suggest that the same mechanism was operative. The pathology revealed by biopsy was minimal in all three cases and not as severe as the liver function abnormalities would have indicated. Complete recovery occurred in all. It is suggested that this reaction may occur more frequently when the dosage of chlorpropamide exceeds 0.5 Gm. daily. Its use should be monitored by periodic determinations of the alkaline phosphatase level for the first six weeks.

2021 Grand Concourse (53) (Dr. Brown).

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JAUNDICE OCCURRING DURING NICOTINIC ACID THERAPY FOR HYPERCHOLESTEREMIA

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The administration of nicotinic acid in dosage of 3 to 6 Gm. a day has proved to be an effective method of reducing serum cholesterol levels. Experience with this medication for periods up to three years has been reported from the Mayo and the Jackson clinics.[1] Except for a few patients in whom there has been a transient abnormality of cephalin-cholesterol flocculation or transaminase, no renal, hematopoietic, or liver abnormalities have been noted.[2] Sulfobromophthalein (Bromsulphalein) tests and liver biopsies have failed to indicate other evidences of toxicity.[3] However, a definite decrease in glucose tolerance with some glycosuria has been noted.[4]

This report is submitted in order to record a case of jaundice occurring during the administration of nicotinic acid and presumably due to intrahepatic cholestasis resulting from drug toxicity.

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Report of a Case

A 23-year-old man was first referred to me in June, 1957, because of an abnormal serum cholesterol level of which he had been aware since he was 17 years of age. He had no symptoms. His mother had died at 40 years of age of a myocardial infarction; his only brother, aged 20, is also known to have a cholesterol abnormality.

Pertinent features of the physical examination revealed a well-appearing, 6 ft. (182.88 cm.), 132 lb. (59.9 kg.) male with dense arcus senilis and xanthomas in the extensor tendons of the fingers, in the Achilles tendons, and in the plantar fascia. An electrocardiogram revealed normal findings. Three serum cholesterol measurements varied from 300 to 350 mg.%.

A 30-Gm. animal fat diet was established, with 3 oz. (85.05 Gm.) of supplemental corn oil administered daily. The patient was not seen again until

October, 1957, at which time his cholesterol level was 373 mg.%. In December, 1957, the administration of nicotinic acid was begun, 1 Gm. three times a day after meals. The remainder of the events in his course, including the side-effects and the laboratory data, are depicted in the figure. It will be noted that there was a prompt decrease of the serum cholesterol level to 225 mg.%, and it was maintained at levels between 150 and 215 mg.% for 40 weeks. When the administration of nicotinic acid was discontinued because of severe itching, the serum cholesterol level quickly returned to more than 400 mg.% then fell sharply again with the reinstitution of nicotinic acid therapy. The decreasing size of one of the fascial xanthomas is depicted in the figure. During the 72nd week, when the patient was first noted to have jaundice and the medication was stopped, the only complaints were of itching and excessive sweating. His appetite and strength were normal and he was afebrile. The liver was palpable 4 cm. below the costal margin but was not tender. Laboratory studies disclosed bile-tinged urine with many granular and cellular casts, a few red blood cells, and no albumin. The complete blood count was normal. Liver function tests revealed a total serum bilirubin level of 7.4 mg.% with a one minute direct of 1 mg.%, alkaline phosphatase of 45 King-Armstrong units, thymol turbidity of 3.8 units, creatinine of 1.04 mg.%, fasting blood sugar level of 74 mg.%, and serum glutamic oxalacetic transaminase level of 91 units. Prothrombin time, reticulocyte count, serology, cephalin-cholesterol flocculation tests and heterophil agglutination time were normal. The patient was hospitalized. During a 20-day period the bilirubin, alkaline phosphatase, and transaminase levels and urinalysis returned to normal and the itching disappeared. The cholesterol also returned to pretreatment levels. No therapy was initiated other than rest and discontinuing the administration of nicotinic acid.

Comment

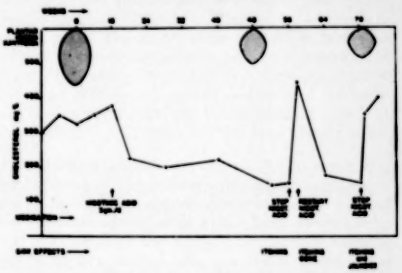
The rationale for the use of nicotinic acid and the physiological mechanisms for reducing serum cholesterol levels are only partially understood.[3] There is good reason to suspect, however, that there are alterations of the enzyme systems of the liver which are involved in cholesterol synthesis and conversion to bile acid.[4] It is conceivable that such alteration of liver activity could result in the kind of liver damage produced by methyl testosterone, chlorpromazine, and other drugs.[7]

Of the 18 other patients in our series currently taking nicotinic acid as a cholesterol depressing agent, no other serious toxic side-effects have been noted. One patient had transient glycosuria. In general there has been a gratifying decrease in serum cholesterol levels and relative concentration of beta-lipoprotein. Certainly in a disease such as familial hypercholesteremia, with its grave potential for early coronary disease, one is justified in using any relatively safe method to reduce serum cholesterol levels. Moreover, it may be possible to remove lipids from tissue deposits, since in this case there was demonstrable reduction in xanthoma size.

Summary

A patient with familial hypercholesteremia and tendon xanthomas exhibited marked reduction in serum cholesterol levels after therapy with large doses of nicotinic acid. The treatment was discontinued after 14 months because of the onset of jaundice, which probably represented intrahepatic cholestasis due to nicotinic acid toxicity.

Veterans Administration Center, Bldg. 114 (25).



Effect of nicotinic acid in large dosage on serum cholesterol levels.

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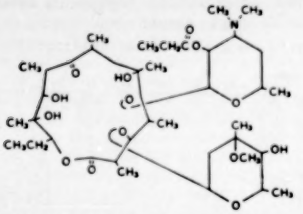
COUNCIL ON DRUGS

NEW AND NONOFFICIAL DRUGS

The following descriptions of drugs are based on available evidence and do not in any case imply endorsement by the Council.

H. D. KAUTZ, M.D., *Secretary.*

Erythromycin Propionate (Ilosone).—Propionyl erythromycin ester.—The propionic acid ester of erythromycin. The structural formula of erythromycin may be represented as follows:



Actions and Uses.—Erythromycin propionate is active against the same pathogenic organisms and has the same uses as erythromycin free base. When administered orally, this ester produces an earlier onset of therapeutic blood levels than does the free base. Blood levels are also higher and of longer duration than those attained with like amounts of the free base. (See the monograph on erythromycin in New and Nonofficial Drugs.)

Dosage.—Erythromycin propionate is administered orally. The usual dose for adults ranges from 250 to 500 mg. every six hours, depending on the severity of the infection. For overwhelming infections, doses as high as 1 Gm. every six hours have been used. In such cases, however, institution of parenteral therapy should be considered. For children up to 50 lb. (22.7 kg.) of body weight, the usual daily dose is 125 mg. every six hours. Heavier children may receive the full adult dose.

Preparations.—capsules 125 mg. and 250 mg.

Year of introduction: 1958.

Eli Lilly and Company cooperated by furnishing scientific data to aid in the evaluation of erythromycin propionate.

Relaxin (Cervilaxin, Releasin).—A factor which produces relaxation of the pubic symphysis and dilation of the uterine cervix in certain animal species. It is a protein or polypeptide of relatively low molecular weight extracted from the ovaries of pregnant sows. Relaxin is assayed biologically.

Actions and Uses.—Relaxin is a naturally occurring substance which is produced by the corpus luteum during pregnancy. Increasing concentrations of relaxin can be detected in the blood and urine of animals and humans during the last two-thirds of the gestation period; it virtually disappears within 24 hours after delivery. The physiological function of relaxin during pregnancy is not known. When given to castrated, estrogen-primed guinea pigs, the drug causes a relaxation of the pubic symphysis. This effect, due to proliferation of capillaries and dissolution of collagen fibers, forms the basis for one of its biological assays. Relaxin has also been demonstrated to inhibit, both in vivo and in vitro, the contractions of uterine muscle in experimental animals. There is some evidence that it effects a relaxing or softening of the uterine cervix of pregnant laboratory animals and humans at term. The relationships, both chemical and physiological, between relaxin and lututrin are far from clear. However, the recent application of countercurrent distribution and chromatographic techniques would suggest the presence in the ovary of at least two distinct factors possessing uterine relaxation activity. One of these factors, relaxin, in addition to this effect on the uterus, also is capable of exerting a pronounced relaxing effect on the pubic symphysis. Since this latter effect is minimal with the second factor, it is conventional to reserve the term "uterine relaxing factor" for lututrin.

The ability of relaxin to inhibit uterine contractions has been demonstrated both in vivo and in vitro in experimental animals and humans. This inhibition is apparently not related to the mechanism of oxytocin stimulation, since the latter will restore uterine contractions even in the presence of relaxin. Further, tokodynamometer studies in humans have revealed a similar effect on uterine motility. Such experiments led to the introduction of relaxin as an agent designed to halt premature uterine contractions between the 29th and 36th week of pregnancy. The multiplicity of factors causing premature labor, the difficulty of identifying true labor, the lack of properly controlled series, and differences in dosage or route of administration of relaxin have all contributed to equivocal results in this indication.

The principal therapeutic interest of relaxin in obstetrics lies in its effects on the uterine cervix. As a result of favorable animal experiments, the drug has been proposed for clinical use as a "cervical softening" agent which is said to shorten the dura-

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tion of full-term labor by facilitating cervical dilation. Although many clinical investigators believe that relaxin exerts a cervical softening effect, there is some disagreement as to its merits in the shortening of labor. On the basis of subjective observations, some obstetricians report that relaxin is effective in easing and shortening labor in the majority of patients, primiparas or multiparas, provided that the cervix is already effaced and dilated at least 2 to 3 cm. at the time the drug is given. Conversely, other investigators, employing more objective clinical methods, have been unable to detect any effect. Part of the confusion in this regard arises as a result of the frequent use of relaxin in conjunction with oxytocic agents for the elective induction of labor at term. However, it would appear from recent controlled experiments that the responsiveness of the uterus to either endogenous or exogenous oxytocin may contribute materially to the effects of relaxin on the uterus. If labor contractions are well established and at frequent and uniform intervals, the administration of relaxin may shorten the course of labor. On the other hand, the administration of the drug to a patient having desultory labor frequently results in a temporary cessation or slowing of the progress of labor. It should be kept in mind that the cervical softening effect of relaxin is of little help in dysfunctional labor or uterine inertia in which the ineffectiveness or weakness of myometrial contractions, and not the degree of cervical dilation, is the factor responsible for the impeded progress of labor. Hence, there seems to be little rationale for the use of relaxin alone in the induction of labor, since oxytocin is necessary to establish good uterine contractions. Its suitability for use in cases of so-called cervical dystocia must await the results of double-blind studies now in progress.

Relaxin has been proposed for use in the treatment of severe dysmenorrhea. The rationale for its use in this indication is based first on tokodynamometer studies, which demonstrate strong uterus motility inhibiting properties in dysmenorrheic patients, and secondly on the cervical softening effect, which has been compared to mechanical dilation of the cervix prior to the onset of catamenial flow that frequently provides relief of pain. Controlled studies now in progress may shed more light on the usefulness of the drug for this purpose.

Among the miscellaneous proposed uses of relaxin is its employment to aid in the expulsion of retained dead fetus and the prevention of hypofibrinogenemia. In one series of cases, the use of large doses of relaxin for cervical softening prior to the use of oxytocin for induction of labor was claimed to be of significance. However, confirmation of this observation in a controlled series is indicated.

One of the experimentally observed effects of relaxin in laboratory animals has been an increase in the elasticity of the skin. Hence, the drug has been tried clinically for the treatment of scleroderma. Some improvement, as evidenced by relief of vasospasm, healing of trophic ulcers, and increase in skin elasticity, has been reported by several authors. Such symptomatic improvement continues as long as relaxin is administered, but the patients usually regress when therapy is terminated.

Since relaxin is a pork protein, it can give rise to sensitivity reactions ranging in severity from chills after its intravenous administration to acute anaphylactoid shock. Although the latter severe reaction has been encountered only rarely, skin testing is advisable for all patients. Except for occasional allergic manifestations, no other side-effects or untoward reactions have been reported.

Dosage.—Relaxin is administered intravenously or intramuscularly. The product is presently assayed by two methods, both of which equate dosage in terms of milligrams. One assay utilizes a guinea pig unit (G. P. U.) which is defined as "that amount of relaxin which produces relaxation of the pubic symphysis in two thirds of a group of 12 or more guinea pigs." The mouse assay is also utilized. This consists of the direct measurement of the interpubic ligament in estrogen-primed immature mice. Since the assay procedures are not precise and the technique of assay varies, the comparative potency of commercial preparations has not been clearly elucidated.

At the present time, precise recommendations for dosage are not possible. However, for cervical softening in normal labor or in cases of cervical dystocia, the proposed doses range from 40 to 120 mg., administered by intravenous drip in 250 to 500 cc. of sterile diluent at rates varying from 4 to 8 cc. per minute. Alternatively, the drug has been injected intramuscularly in doses of 40 mg. every two hours for three doses.

When used in conjunction with oxytocic agents for the elective induction of labor, the drug is administered by intravenous drip after rupture of the membranes. The dosage is that outlined previously for normal labor.

Although the clinical evidence to support its efficacy in premature labor is equivocal, relaxin has been administered intramuscularly in doses of 40 mg., followed by 20 mg. every two hours. It has also been given intravenously in doses of 40 to 80 mg., in 1,000 cc. of 5% dextrose in water for injection at a rate of 4 cc. per minute.

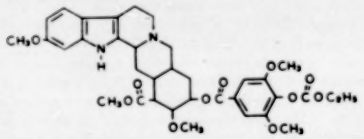
Proposed intramuscular doses for other claimed uses of relaxin are as follows: for dysmenorrhea, 20 mg. every four hours; for scleroderma, initially 20 mg. per day until therapeutic effects are known, followed by the lowest doses compatible with continued improvement; for delivery of retained dead fetus, 320 mg. in six doses over a period of 12 hours. Until more evidence of clinical efficacy appears in the literature, the foregoing proposed doses are considered experimental.

Preparations.—solution (injection) 20 mg. in 1 cc., 40 mg. in 2 cc.

Year of introduction: 1956.

The National Drug Company and Warner-Chilcott Laboratories, Division of Warner-Lambert Pharmaceutical Company, cooperated by furnishing scientific data to aid in the evaluation of relaxin.

Syrosingopine (Singoserp).—Carbethoxysyringoyl methyl reserpate.—Syrosingopine is prepared from reserpine by hydrolysis and reesterification. The structural formula of syrosingopine may be represented as follows:



Actions and Uses.—Syrosingopine is proposed for use as an antihypertensive agent and is closely related chemically to reserpine. (See the monograph on reserpine in New and Nonofficial Drugs.) When equal doses of the two drugs are compared, syrosingopine is both less potent and less toxic than reserpine. The two probably have about the same margin of safety.

Syrosingopine depresses the blood pressure in anesthetized and unanesthetized normotensive dogs, neurogenic hypertensive dogs, and in rats with adrenal regeneration hypertension. In dogs, the hypotensive effect is accompanied by a reduction in heart rate of 15 to 20%. It also reduces the rate of the isolated heart without altering the force of contraction or the coronary blood flow. It obtunds the carotid occlusion reflex.

Small doses of syrosingopine in dogs produce miosis, slight respiratory stimulation, and relaxation of the nictitating membrane. Larger doses produce sedation. It is one-twentieth as potent as reserpine in depressing the spontaneous activity of mice and one-tenth as potent in impairing the performance of monkeys in a discrimination learning task. Syrosingopine stimulates the secretion of hydrochloric acid in the denervated Heidenhain pouch of the dog but is less active in this respect than reserpine.

Clinically, syrosingopine alone is effective in some cases of mild or moderate labile hypertension. However, as is the case with all Rauwolfia compounds, syrosingopine generally will not provide satisfactory control of severe hypertension unless it is used in conjunction with more potent antihypertensive drugs. When given in combination with such agents, syrosingopine may make it possible to reduce their dosage.

Chronic toxicity studies in animals have disclosed no serious adverse effects on the bone marrow, liver, kidney, or other tissues. Side-effects reported in the clinical usage of the drug are similar to those of other Rauwolfia alkaloids. The most frequent of these is nasal congestion, followed closely in order of incidence by gastric complaints, drowsiness, and fatigue. Less frequently reported symptoms include headache, increased dreaming, emotional depression, and skin eruption.

To date, syrosingopine has been used only for the management of hypertension. Its advantages and limitations appear to be similar to those of other Rauwolfia drugs. Although early reports indicate that side-effects may be less troublesome than with other members of this group, a definitive assessment of the efficacy and toxicity of syrosingopine relative to the parent substance reserpine and other antihypertensive agents must await further clinical trial.

Dosage.—Syrosingopine is administered orally. The optimal dose (i. e., that which produces the best control of blood pressure without prohibitive side-effects) must be carefully determined for each patient. The suggested initial dose is 1 mg. per day. Since the effects of syrosingopine are manifested only slowly, it is advisable to maintain the initial dosage for a period of two weeks. Then, if there is inadequate clinical response, the daily dose may be gradually increased up to 3 mg. (in divided amounts), provided that each increase is maintained for a sufficient period to establish the level at which untoward effects appear. Occasionally, a patient may tolerate a higher daily dose.

Preparations.—tablets 1 mg.

Year of introduction: 1959.

Ciba Pharmaceutical Products, Inc., cooperated by furnishing scientific data to aid in the evaluation of syrosingopine.

REGRESSION OF DISEASES.—A communicable disease may spread throughout an area from one or more foci, and then gradually recede, even without effective treatment, until it is again confined to a few foci, or even disappears. Trachoma, for example, was brought into Europe by Napoleon's army on its return from Egypt, and ravaged the entire continent; but it has now practically disappeared from most European countries. Yaws has similarly almost disappeared from Ceylon, where in 1916-1920 there were 30,000 to 35,000 people with yaws lesions attending the outpatient departments of hospitals every year.—Yaws: Disease in Regression, *WHO Chronicle*, May, 1959.

COUNCIL ON FOODS AND NUTRITION

The Council has authorized publication of the following report.

PHILIP L. WHITE, SC.D., *Secretary.*

PROBLEM OF ANTIBIOTICS IN FOODS

Henry Welch, Ph.D., Washington, D. C.

In the United States antibiotics are probably our most important and most widely used therapeutic agents, and it is unlikely that any one of us will pass from "cradle to grave" without having one or more administered to us for some sound medical reason.

Background to the Problem

In 1957, total antibiotic production was over 2,500,000 lb., and it probably need not be emphasized here that these drugs have had wide and, in some cases, indiscriminate use. Their remarkable curative powers, more pronounced perhaps in the early days than now, resulted in their being injected, insufflated, given by mouth, spread on every part of the body, and sprayed intra-abdominally, intracisternally, intrapleurally, and intravaginally; no surface or cavity of the body has remained inviolate.

There are now over 400 preparations of antibiotics available for clinical use, and they run the gamut of injectables, ointments, powders, sprays, capsules, syrups, ear and eye drops, suppositories, troches, and tablets. Antibiotics have saved tens of thousands of lives in the past 15 years, and the reduction in the rates of mortality, morbidity, and complications of diseases has affected the lives of millions. Nevertheless, with such major advances in therapy and consequent wide use (not to mention indiscriminate use), unfortunately we have to face the accompanying untoward side-reactions that invariably follow. In the case of penicillin, a relatively atoxic drug, the "side-reaction" is its potentiality for sensitizing certain individuals. Although the other antibiotics are, in general, poor sensitizers, other side-reactions may occur after their administration. Thus, we have the initial provocation brought about by the extensive therapeutic and prophylactic use of a group of very valuable drugs.

Unfortunate Reactors

It is estimated that about 10% of the population in the United States has a tendency to become sensitive in the course of a lifetime to some food, drug, cosmetic, or other substance. Within this group of people there is a great variation in susceptibility to sensitization. Some acquire it easily, whereas others are more resistant. Some may be sensitive on first contact (the atopic group), while others require at least one contact, and still others may require several contacts before exhibiting a reaction. The reactions, too, vary in degree from mild, transient rashes to prolonged urticaria, and from a brief asthmatic attack to fatal anaphylactoid shock. Fortunately, these serious allergic manifestations occur less frequently in children to whom tons of antibiotics are administered yearly.

Since the population of the United States is estimated at over 175 million, we are concerned primarily with perhaps 17 to 20 million individuals who may react to contact with antibiotics—through proper therapeutic use or, inadvertently, through eating or drinking foods containing them. In the first case, the physician and patient have a choice, but in the latter instance there is none.

Introduction of Antibiotics in Foods

The extension of the uses of antibiotics to fields other than for prevention and treatment of human disease has magnified the problems of the physician from the standpoint of the side-reactions he may encounter in his daily practice.

Antibiotics are used in animal nutrition for promotion of growth in swine, chicks, and poults. Therapeutic and prophylactic use of large quantities of antibiotics is made for animals such as cows, beef cattle, swine, and chicks. These drugs are now being used as crop sprays to prevent blight in apples, pears, walnuts, and beans and to combat bacterial diseases of tobacco, tomatoes, peppers, and cherries. Two antibiotics, chlortetracycline and oxytetracycline, have been approved for use as preservatives on poultry and fish. A number of studies have been made to demonstrate their effectiveness as preservatives for vegetables, beef, ham, and other perishables.

The actual or potential introduction of antibiotics into the food supply poses the same problem as does the use of any other chemical. This grow-

Director of Division of Antibiotics, Food and Drug Administration, U. S. Department of Health, Education, and Welfare.

ing use of chemicals in food is one of the most serious problems facing public health authorities today, increasing the complexity of diagnosis and treatment immeasurably. It should be emphasized, however, that the problem of contamination of foods with antibiotics is very small when compared with other potential chemical contaminants of food. There is virtually no limit to the expanding list of chemicals that may find their way into our food supply. Chemicals are promoted as stabilizers, preservatives, disinfectants, antioxidants, extenders, tenderizers, emulsifiers, growth promoters, fumigants, herbicides, defoliants, fungicides, miticides, bleaches, sweeteners, conditioners, colors, and flavors. In addition, food packages that incorporate new plastics, enamels, films, plasticizers, catalysts, and coatings are further potential sources of food adulteration.

Uses of Antibiotics

Animal Feed.—Antibiotics are used in animal feed for growth stimulation and for the prevention and treatment of disease. The quantities of antibiotics authorized by the Food and Drug Administration in such feeds range from 5 to 200 ppm. When these medicated feeds are used in the manner prescribed by the FDA, there are no drug residues in the meat, eggs, or milk of treated animals. Therefore, when such feeds are properly used, they do not constitute a public health hazard. However, there is always the possibility of misuse.

Crop Sprays.—Antibiotics used as crop sprays are dissipated before the edible portion of the plant is formed, and, since they do not reach the consumer, no public health problem is involved.

Food Preservation.—Extensive experiments have been conducted to explore the potentialities of antibiotics as food preservatives. In November, 1955, the FDA approved the use of chlortetracycline for the preservation of raw poultry. Approximately one year later similar approval was given for oxytetracycline. Tolerance levels for these drugs were established under the provisions of the Miller Pesticide Chemicals amendment to the federal Food, Drug, and Cosmetic Act, passed by the 83rd Congress in 1954. These drugs act as preservatives and extend the "shelf life" of the fowl. Under the Miller amendment, the applicant must demonstrate "usefulness" to the satisfaction of the United States Department of Agriculture and "safety" to the FDA.

The tolerance level in the raw bird for both chlortetracycline and oxytetracycline was established at 7 ppm in any part of the bird. (This is about 1.5 mg. per serving of a one-half pound.) However, before approval of this tolerance level was granted, it had to be shown that no antibiotic residues could be found in the poultry after cooking by broiling, frying, boiling, or baking. In April, 1959, a tolerance level of 5 ppm was established for chlortetracycline in certain kinds of raw fish and shellfish.

A considerable number of investigations of the usefulness of antibiotics in the preservation of meats also have been completed. However, approval of this use by the establishment of tolerance levels under the Miller amendment have not been granted as yet and can be obtained only when conclusive evidence is presented that such use is not detrimental to the health of the general public.

Indirect Antibiotic Adulteration of Milk

In addition to being directly introduced into the food supply, antibiotics also may find their way indirectly into foods. In 1948, it was noted that milk from cows treated for mastitis with penicillin by intramammary infusion often failed to produce a satisfactory cheese product. This was due to the inhibition of the starter culture used in cheese manufacture by the antibiotic present in the milk.

Realizing that antibiotics might also reach the consumer by way of milk, the FDA required that mastitis preparations carry a warning in their labeling to the effect that "milk from treated segments of udders should be discarded or used for purposes other than human consumption for at least 72 hours after the last treatment." In further recognition of the possibility that antibiotics might get into the food supply, a statement of policy was issued in February, 1953, by the Secretary of the U. S. Department of Health, Education, and Welfare concerning the direct or indirect addition of antibiotic drugs to foods for human consumption. In effect, the policy statement was as follows: "The presence of antibiotic drugs in foods intended for human consumption, or the direct or indirect addition of such drugs to such foods, may be deemed an adulteration within the meaning of section 402 of the Federal Food, Drug, and Cosmetic Act."

Very large amounts of antibiotics are used in the treatment of milk-producing cows infected with mastitis. It is estimated that more than 75 tons of these drugs is used yearly in the treatment of this widespread infection. The great bulk of infected cows are treated by udder infusion, for which purpose a variety of products are available. Penicillin is used in perhaps the greatest volume. However, other antibiotics, such as dihydrostreptomycin, streptomycin, the tetracyclines, neomycin, polymyxin, and bacitracin, as well as the sulfonamides, are used for treatment and prophylaxis. Experience has shown that the entire amount of infused antibiotic or sulfonamide is eliminated by regular milking over a period of three days. It appears that failure to observe the warning given in the labeling of mastitis preparations concerning the discarding of milk from treated cows is largely responsible for the antibiotic residues that may be present in the milk supply.

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V.

During the years 1954, 1955, and 1956, three surveys were made to determine the antibiotic content of fluid market milk. In these surveys, conducted by the FDA, U. S. Department of Health, Education, and Welfare, a total of 2,274 samples were examined. Every state in the United States was included in these investigations. An average of 6.9% of the samples examined contained penicillin in concentrations varying from 0.003 to 0.550 units per milliliter. Other dairy products tested, including powdered milk, evaporated milk, ice cream, butter, cheese, shell eggs, and broken eggs, were found to be free from antibiotic residues.

Recent Advances in Antibiotic Problem

About one year ago a medical advisory panel accepted the invitation of the Commissioner of the FDA to consider the public health problems involved by the presence of antibiotics in market milk. The members of the advisory panel were Drs. Wesley W. Spink, chairman, University of Minnesota; Harry F. Dowling, University of Illinois; Samuel M. Feinberg, Northwestern University; Chester S. Keefer, Evans Memorial Hospital, Boston; Perrin H. Long, State University of New York; Walsh McDermott, Cornell University Medical College; Robert Popper, Veterans Administration Hospital, Memphis, Tenn.; and Bernard B. Siegel, Jewish Hospital of Brooklyn. After an all-day session, during which the problems involved were discussed thoroughly, it was apparent that our main health problem was concerned with penicillin, even though the other antibiotics used in mastitis preparations were found in approximately 1% of the samples examined. It was the consensus of the panel that these antibiotics—the tetracyclines, streptomycin, dihydrostreptomycin, bacitracin, polymxin, and neomycin, which may be found in mastitis preparations, did not at that time pose a public health problem.

It was agreed that penicillin is a very active, antigenic substance and, even in the low concentrations found in milk, might well cause reactions in highly sensitive individuals. It was apparent that the physician should be most concerned in his practice with the latter persons who constitute something less than 10% of the population. It seemed certain that in these individuals reactions could occur. Such reactions could vary in intensity from mild transient ones to possibly serious ones, the serious reactions occurring in those individuals exquisitely sensitive to penicillin. Because scientific proof is essential, it was the consensus of the panel that further studies were necessary with highly sensitive human volunteers to determine whether the ingestion of milk containing those concentrations of penicillin now found in some market milk would cause allergic manifestations.

Recently, the FDA has taken three steps to alleviate the public health problem involved: 1. Through cooperation with the U. S. Department of Agriculture, an intensive program has been initiated to educate the farmer concerning the importance of discarding, or using for purposes other than human consumption, milk from cows treated for mastitis with antibiotic drugs for a period of three days following the last treatment. In addition, the National Milk Producers Federation, which includes some 500,000 farmers, is assisting in this educational program through their state agents. 2. On Jan. 23, 1957, a notice was published in the *Federal Register* concerning the warning statement that is required in the labeling of antibiotic drugs intended for intramammary infusion. It was proposed that for greater conspicuousness this warning be placed on the immediate container of the drug rather than in the literature accompanying it. This is now required. 3. On Feb. 9, 1957, a "Notice of Proposed Rule Making" was published in the *Federal Register*, limiting the penicillin content of mastitis preparations to 100,000 units per dose. This became effective on Aug. 12, 1957.

In the fall of 1958 and the winter of 1959, a fourth nationwide survey of milk was conducted by the FDA to determine if the program discussed above had reduced or eliminated antibiotics from our milk supply. A total of 1,170 samples of raw milk was collected from tank trucks after pickup from dairy farmers or directly from individual producers. Each sample was examined for residues of penicillin, streptomycin, the tetracyclines, bacitracin, polymyxin, and neomycin, all of which are used in the treatment of mastitis in dairy animals. Penicillin, as confirmed by the penicillinase identity test, in concentrations of 0.006 to 1.22 units per milliliter, was found in 43 (3.7%) of the samples. One penicillin-positive sample also appeared to contain streptomycin. Twenty-two additional samples appeared to contain one of the tetracyclines, and one other sample contained bacitracin-like activity. However, there are no specific identity tests for small quantities of these drugs and, therefore, their antibacterial activity cannot unequivocally be attributed to these antibiotics. The results of this most recent survey indicate that the program that was initiated after the third survey has caused a significant decrease in the incidence of penicillin-contaminated milk. In fact, this decrease may be even greater than that shown by the figures because of the difference in sampling techniques used in the 1959 survey and in the previous surveys. In the first three surveys, all samples were collected from milk that had been processed by the dairies and had been delivered to the retail trade. We believe that many of the penicillin-positive samples found in the fourth survey would have

been negative if they had been collected after having been diluted with antibiotic-free milk at the dairy, which normally would have been the case. However, the program has not solved completely the problem of penicillin-contaminated milk. It is therefore necessary that other approaches be considered as a solution to this public health problem.

Summary

There are 17 to 20 million individuals in the United States who may react to contact with antibiotics. The physician can avoid unfavorable side-reactions in these people by the discriminate use of antibiotics as therapeutic agents. A greater problem for the physician is the introduction of antibiotics in foods, both directly and indirectly. Antibiotics are used in animal feeds, crop sprays, and as food preservatives. The FDA and other agencies have taken steps to alleviate this problem; however, it has not been solved completely.

ANNOUNCEMENT

A monograph of the five papers presented at the symposium on "Nutrition in Pregnancy" in Columbia, Mo., Oct. 11, 1957, is now available. These papers, which were published in THE JOURNAL, include "Nutritional State of the Mother Prior to Conception" by Genevieve Stearns, Ph.D.; "Maternal Nutrition and the Fetus" by Ray Hepner, M.D.; "Production of Congenital Malformations by Dietary Measures (Experiments in Mammals)" by Josef Warkany, M.D.; "Vanderbilt Cooperative Study of Maternal and Infant Nutrition: XII. Effect of Reproductive Cycle on Nutritional Status and Requirements" by William J. McGanity, M.D., F.R.C.S.(C), Edwin B. Bridgforth, A.B., and William J. Darby, M.D., Ph.D.; and "Metabolic and Biochemical Changes in Normal Pregnancy" by Icie G. Macy, Ph.D., Sc.D. The "Nutrition in Pregnancy" monograph may be obtained, free of charge, from the Council office.

COUNCIL ON MEDICAL PHYSICS

Report to the Council

The Council has authorized publication of the following report. The conditions treated and dosages used represent the author's research and experience. They should not be construed as recommendations of the Council, since the final decision as to dosage and use must rest with the individual practitioner who has examined the patient to be treated. Ionizing radiation for ophthalmic conditions should be employed only by those who are experts and are well aware of the dangers of this form of treatment to the patient and to the physician.

RALPH E. DE FOREST, M.D.,
Secretary.

BETA RADIATION SOURCES, USES, AND DANGERS IN TREATMENT OF THE EYE

William F. Hughes, M.D., Chicago

Beta radiation from radium, radon, and radium D-E has been used in the treatment of certain external ocular conditions for about 40 years because of the relatively superficial effects and accurate localization of the radiation. More recently, radioactive strontium (Sr^{90})-yttrium (Y^{90}) applicators have become available as a source of beta particles or electrons for ocular use. The early enthusiastic reports of the efficacy of beta radiation have been tempered by the appearance of certain secondary complications including cataract. Therefore, it becomes more important that the clinician be aware of the sources, rationale, uses, contraindications, dosages, and dangers of beta therapy.

From the Department of Ophthalmology, University of Illinois College of Medicine.

Characteristics of Various Sources of Beta Radiation

Various sources and applicators have differing characteristics in surface output, depth dose, and amount of gamma rays. A comparison of available data [1] on these applicators is given in table 1. The differences in the construction of the applicators, their output, and depth doses are readily apparent. The earlier method of denoting dosages as "gram seconds" or "millicurie minutes" has no meaning unless the individual applicator is standardized, either physically by means of the Failla-type extrapolation (vanishing ion) chamber or biologically on animal and human eyes. Not only are the outputs of different types of applicators with similar amounts

of radioactive material different, but applicators of similar design and materials may show significant variations.

Surface Output.—In the past, surface output has been denoted physically as so many reb (roentgen equivalents beta) or rep (roentgen equivalents physical) per second, representing an energy absorption by air of 84 ergs per gram of air per second, or an energy absorption by tissue of 93 ergs per gram of tissue per second. More recently, a new unit of dosage has been officially adopted; namely, a rad, indicating an energy absorption of 100 ergs per gram. Accordingly, for Sr^{90}, 1 rad = 1.19 rep (air) or 1.08 rep (tissue). These numerical values should be considered as guides to clinical dosage rather than be accepted as absolute values. Possible variables include the following factors.

1. Uneven distribution of the radioactive substance on the inner surface of the applicator may produce a greater error with the extrapolation chamber than with depth doses determined by photographic film determinations. Such unevenness can be detected by underexposing a photographic film with the active surface of the applicator.

2. Filtration by the radioactive material itself (especially radium or radium D-E) or by the window of the applicator can (*a*) increase the depth dose by filtering out beta particles of less energy, although the rad surface output as measured by the extrapolation chamber may be the same, or (*b*) produce more scatter, affecting the extrapolation chamber more than the film method.

3. The surface output is calculated by extrapolation to zero volume of the ionization chamber, successive readings having been taken of the amount of ionization per unit volume produced by the applicator in progressively smaller quantities of air. Estimation of the ionization in "zero volume" is made from the slope of the curve as volume in the ionization chamber is reduced. Unfortunately, the slope of this curve is constantly changing, and the extrapolated estimate of surface output can be as much as 10% in error.

4. Changes in technique of the extrapolation chamber measurements have been made in the past in an effort to approach an absolute value. This has led to confusion in the clinical use of the strontium applicator based on previously established dosages. Recently, this difficulty has not been experienced in restandardization of the applicators.

5. Leakage of radioactive material can occur, resulting not only in loss of potency of the applicator but also in radiational hazard in the environment. This can be tested for by "wipe tests" such as those in which the surface of the applicator is wiped seven times on filter paper, which is then tested for radioactivity with a Geiger tube. The Geiger tube should have a window thickness resulting in a weight of less than 2 mg. per square centimeter. Under regulations of the Atomic Energy Commission, one would not be authorized to purchase a Sr^{90} applicator unless adequate facilities existed for carrying out a wipe test. Sr^{90} applicators should be rechecked and restandardized, especially if there has been a positive wipe test. The user should also be warned to keep his hands from the front of the applicator when wiping the surface. It is also a good idea to attach to the storage box a decay curve showing the activity over one half-life, e. g., 25 years for the Sr^{90} applicator.

How can an ophthalmologist or radiologist be certain of the clinical effect to be expected from a certain applicator? Evenness of layering of the radioactive material can be checked with x-ray film. The surface output and depth doses can be determined on each applicator by the company which

TABLE 1.—*Comparison of Various Sources of Beta Radiation*

Characteristic	Radium		Radon		Radium D-E		Sr^{90}-Y^{90}	
Applicator	Krohmer	Iliff	Burnham (glass bulb)	Hughes (glass needles)	Swanberg		Commercial Applicator No. 1	Commercial Applicator No. 2
Quantity of radioactive material	25 mg.	50 mg.	50-400 mc.	50-300 mc.	10 mg.	20 mg.	25-100 mc.	50 mc.
Size of active surface, mm.	6-8	6x12	4-5	5x7	6-8	6-8	5-7.8	8-7
Inherent filtration	0.1 mm. thickness of magnesium	0.1 mm. thickness of monel	0.1 mm. thickness of glass (approx.)	0.1 thickness of glass (approx.)	0.05 mm. thickness of aluminum or 0.1 mm. thickness of magnesium	0.5 mm. thickness of aluminum or 0.01 mm. thickness of magnesium	0.05 mm. thickness of stainless steel and 0.25 mm. thickness of aluminum	0.1 mm. thickness of stainless steel
Surface output	37 rad.*/sec.	†	0.14-0.5 rad./sec./mc. ave.=0.4 rad./sec./mc.	2-3 rad./sec./mc. (est.)‡	3 rad./sec.	4.4 rad./sec.	approx. 25 rad./sec.-84 rad./sec.	approx. 50 rad./sec.
Part of radiation reaching tissue at depth of:								
1 mm., %	†	17	30-50	†	10	†	41-55	55
2 mm., %	†	8	6-25	†	1	†	19-25	32
3 mm., %	†	4	3-10	†	0	†	7-16	18
4 mm., %	†	2	2-5	†	0	†	4-6	6.5
5 mm., %	†	1	0.8-3	†	0	†	1-3	4
Gamma rays	†	>3.5%	approx. 3.5%	†	none	none	none	none

* Rad.=unit of absorbed dose.
† Data not available.
‡ Estimated by effects on tissues in comparison with other applicators which have been standardized by physical methods.

issues the applicator. Biological standardization is the only means at present of determining the output of applicators with unusual shapes and is a valuable check on the physical methods of measurement. This can be performed on the rabbit cornea. The applicator is placed in steady contact with the rabbit cornea, preferably using six corneas for each dose of 15,000, 20,000, 25,000, and 30,000 rad. The minimal dose that produces a faint corneal opacity which does not clear for several weeks has been termed the "Minimal Inflammatory Dose" or "MID" by Wilson. For the Sr^{90} applicator, this is approximately 21,000 rad ± 10%.

Depth Doses.—Surface output does not necessarily indicate clinical effectiveness or possible dangers of cataract formation. Because true absorption or ionization in tissue cannot be measured directly, a measurement in the ionization chamber can be made after the beta particles have passed through varying thicknesses of tissue-equivalent material, for example, polystyrene, lucite, or water. Ideally, selection of beta sources with beta particles of different energies and depth doses might be made with regard to the depth of the lesion to be treated. For

TABLE 2.—*Relative Proportion in Tissues of Beta and Gamma Radiation from Radon*

Tissue Depth, Mm.	Beta Radiation, %	Gamma Radiation, %
0 (Surface)	96.5	3.5
1	88.0	12.0
2	78.5	21.5
3	67.6	32.4
4	55.5	44.5
5	43.0	57.0

example, prevention of the superficial vascularization of a recurrent pterygium would require only surface irradiation, whereas deeper irradiation would be indicated for tumors or deep corneal vascularization. Knowledge of depth doses is also important in relation to possible formation of cataract. In applying contact therapy to the corneal limbus, the sensitive equatorial cells of the lens are only 3 mm. away, whereas the anterior surface of the lens is usually about 4 mm. distant from the apex of the cornea. With this information, an estimate can be made of the amount of radiation reaching the lens. The tolerance of the lens for irradiation will be discussed under dangers of beta radiation.

Gamma Rays.—Radium and radon applicators, unlike radium D-E and Sr^{90} applicators, emit gamma radiation in addition to beta radiation. The relative proportion of beta to gamma radiation from radon at various tissue levels is found in table 2. Because of the relatively small amount of gamma radiation in comparison to the beta particles which emerge from radon, a therapeutic dose of beta radiation can be applied to superficial tissue without undue gamma ray absorption in the deeper structures of the eye. The percentage of gamma rays is somewhat greater in radium than in radon applicators because of the absorption of beta particles by the radium mass itself. This results in a loss of clinical potency of beta radiation from the radium applicator, which might be roughly estimated as 15% per unit area for the Iliff applicator. Accordingly, with the radium applicator, a longer exposure time, with consequently more gamma radiation, is necessary to obtain the desired dosage of beta radiation than is the case when radon is used. From a practical standpoint, gamma radiation from beta applicators creates some hazard for the therapist. These applicators should be stored in a lead container with walls, top, and bottom at least one inch in thickness. The lids should be held open by a speculum, by the patient, or by another person not connected with radiation therapy. The maximum permissible dose for the therapist should follow the recommendations of the National Committee on Radiation Protection.[2]

Characteristics of Applicators.—In an effort to encourage more uniformity of beta radiation applicators, certain information about the characteristics of each applicator is desirable, as follows: (1) the quality of radioactive emanations, including the ratio of beta to gamma rays and energy of the beta particles (maximum Mev, average Mev, and depth doses); (2) certification by the National Bureau of Standards or by a qualified laboratory of the quantitative output of each individual applicator in rad surface output; and (3) experimental and clinical trials to corroborate the output.

With the need for the information just outlined, a few comments on the deficiencies of the various applicators are in order. In the radium applicators, the surface output in rad per second has not been standardized physically, the depth doses have not been determined, and biological determination of the MID has not been published.

A specimen of an early model radium D-E applicator was tested for surface output and depth dose, but each individual applicator has not been standardized. Wilson [14] found that the radium D-E applicator required approximately two and one-half times the dose in gram seconds of radon to produce similar clinical effects in both rabbit and human eyes. This lower clinical potency of the radium D-E applicator is probably the result of the self-absorption of the relatively soft beta particles by the radium D mass itself, plus the smaller depth doses of the less energetic beta particles. Doubling the quantity of radium D in the applicator does not double the output but instead increases the effectiveness by approximately 50%. Because of the relatively low output of the 10-mc. radium D-E applicator, either prolonged treatment times up to 16 minutes are required to eliminate such a condition as superficial corneal vascularization, or repeated exposures within relatively short periods of time (e. g., every week) are required to obtain adequate cumulative effects. These considerations

are of some practical importance clinically, because prolonged treatment times increase the difficulty of accurate localization of the radiation and increase the amount of trauma. The relatively low depth dose makes it difficult to obtain adequate dosage in the treatment of such conditions as deep corneal vascularization without excessive damage to the superficial tissues.

The radon applicators have the inherent disadvantage of deterioration (half-life, 3.825 days), and it is practically impossible to standardize each applicator after reloading. Krohmer [14] measured several radon applicators physically and found that the surface output varied as much as 63%. Also, the construction and shape of some radon applicators have prevented measurement of the output by ionization chambers.

The characteristics just outlined for each applicator are available for Sr^{90} applicators. This assumes that the present physical methods of calibrating the applicators by the issuing companies remain the same, and that one rad surface output today will correspond to one rad surface output on which the clinical dosages have been determined previously.

Use of Beta Radiation

The general uses for beta radiation are the same as for any other type of radiation such as x-ray. The effects of irradiation are destructive, and there must be a differential sensitivity between the pathological cells to be destroyed and the normal cells of the adjacent tissue. The relative sensitivity of cells to radiation has been determined previously by Desjardins [3] and others in the following order of decreasing sensitivity: lymphoid cells, polymorphonuclear cells, eosinophils, epithelium (conjunctiva, cornea, lens, and ciliary), endothelium (vessels, cornea), connective tissue including the cells of the corneal stroma, muscle, bone, and nerve which includes the neural elements of the retina. Among other factors which increase the sensitivity of cells are undifferentiation, immaturity, premitotic stage, active metabolism, and a large blood supply. Very small doses of irradiation are stated to affect favorably infectious processes, although larger doses are detrimental.

Method of Administration.—The method of administration of beta radiation is as follows. Slit-lamp examination is performed to determine the exact area for treatment. Topical anesthesia is then applied and the applicator placed in contact with the lesion. Unless the total dose is purposely fractionated or a severe condition warrants more frequent treatments, at least two to three months should be allowed between treatments in order to observe the maximal beneficial effects of the previous treatment and thus utilize the smallest effective dose. However, as shown in other sections of this paper, determination of maximal deleterious effects requires a greater time interval. When the Sr^{90} applicator is employed, probably not more than 4,000 rad per area of treatment should be used, unless the possibility of later lens opacities is considered to be a legitimate risk. A dose of 1,000 rad may be sufficient for highly sensitive lesions.

Conditions Treated.—Because of the uncertainties in dosage and the development of late complications, beta radiation should be reserved for use in those conditions in which it is superior to other methods of treatment or in which other methods have failed. This conservatism has reduced the number of conditions in which beta radiation is recommended. It is not the purpose of this communication to give in detail the dosages and results of beta radiation therapy in many conditions. Recently, a study has been made of 694 eyes previously treated with radon (60% of cases) or a Sr^{90} applicator.[4] In about half of the cases patients were followed up for over five years, and in some of the early cases patients treated with radon were followed for as long as nine years. In general, the results of treatment and the complications were essentially the same, whether a Sr^{90} applicator or a radon applicator [14] had been used. As an approximation of dosages of equal clinical effectiveness, one gram second of beta-radon was roughly equivalent to 2,000 rad with the Sr^{90} applicator. The currently recommended dosages in rad given subsequently apply to the Sr^{90} applicator.

Favorable Results of Treatment with Beta Radiation

Corneal Vascularization.—The undesirability of corneal vascularization and the relatively great sensitivity of the endothelium of blood vessels to radiation have led to the use of beta radiation in preventing or eliminating corneal vascularization. In general, superficial vessels are more sensitive to treatment, probably because they receive a larger dose of radiation. Small, actively growing capillaries on the surface are very sensitive, thereby providing an effective means of preventing recurrences of pterygiums after operation. Large trunk vessels, especially when deep, require such large doses of radiation that the long-term results are usually disappointing. The most gratifying results both subjectively and objectively were obtained in cases of rosacea keratitis, which were resistant to local corticosteroid therapy, in which only 2 out of 42 patients remained unimproved and none became worse after radiotherapy. The effective dose in any one quadrant of the cornea necessary to eliminate the corneal vascularization of rosacea keratitis approached the minimal dose which might produce small peripheral opacities in the lens a few years later, namely, 6,000 rad. The primary treatment of pterygiums or their recurrences by beta radiation required unduly large doses to eliminate the well-established vessels. However, beta radiation given within one to two weeks after operation appeared

effective, with only 1 case of 42 recurrent cases of pterygiums recurring after this combined treatment; none of 81 cases of primary pterygiums treated with surgery and prophylactic beta radiation developed any recurrence. Although a larger series with proper controls is required for final evaluation, the present management for very vascular or recurrent pterygiums consists of operation, followed one week later with 1,000 to 2,000 rad of beta radiation, repeated once one to three weeks later.

Limbal Tumors.—All 22 cases of tumors at the corneoscleral junction responded well to beta radiation, either with or without partial excision, including papillomas, epithelial plaques, Bowen's disease (epidermoid carcinoma in situ of skin), and epitheliomas (11 cases). A dose of 5,000 rad is recommended for premalignant and malignant tumors, and 3,000 rad for papillomas.

Vernal Catarrh and Allergic (Phlyctenular) Keratitis.— Vernal catarrh and allergic conditions of the conjunctiva and cornea are usually alleviated by the local use of corticosteroids such as hydrocortisone or prednisolone. However, certain cases do not respond satisfactorily or have frequent recurrences. This is particularly true of palpebral vernal catarrh, with large pavement-stone vegetations and ropy discharge, and of allergic keratitis of the lower portion of the cornea associated with superficial vascularization. The effects of beta radiation have been helpful in most of these cases. In general, doses of 5,000 rad are given to each area of the vernal catarrh on the upper lids, care being taken not to expose the roots of the lashes. Such doses can be repeated once or twice, if necessary, after several weeks or a few months. For limbal lesions of this type, doses as low as 1,000 to 2,000 rad, perhaps repeated once after a few weeks, may be sufficient to eliminate this allergic type of tissue and superficial vascularization.

Conjunctival Papillomas and Hemangiomas.— These benign tumors are very sensitive to beta radiation and can often be eliminated by doses as low as 2,000 rad.

Trichiasis.—The dosage required for permanent epilation is uncertain, but it can usually be accomplished by 3,000 rad of beta radiation. However, the eyeball should be carefully shielded.

Variable Results of Treatment with Beta Radiation

Good results were obtained in only 30 to 40% of the following types of corneal vascularization: primary vascularizing keratitis, indolent corneal ulcer, chemical burns, effects following corneal transplantation, scars of unknown etiology, trachoma, corneal dystrophy, and keratoconus. Six cases of interstitial keratitis showed no change attributable to the radiation. Although various types of keratitis, episcleritis, and scleritis often showed improvement after treatment with very low doses (500 to 1,000 rad) of beta radiation, it could not be determined whether this was significantly related to the radiotherapy. Although granulation tissue is sensitive to radiation, the results after beta radiation therapy were variable, possibly because the depth dose was insufficient to reach the deeper portions of the granulation tissue usually located within the tarsus of the lid. Therefore, it is inadvisable to use this radiation to treat such granulation tissue. Merriam [5] reported that precancerous melanosis of the conjunctiva responds satisfactorily to 3,000 to 5,000 rad of beta radiation.

Contraindications for Use

Beta radiation should not be used for several conditions because of lack of effect, better treatment available, or undesirable complications. These include tumors of the lid margin, nevi of the conjunctiva, pinguecula, primary treatment of pterygiums without immediately preceding surgery, pemphigus, corneal scars without vascularization, Fuchs' endothelial-epithelial dystrophy, epithelial downgrowths into the anterior chamber, acute chemical burns, and inflammatory lesions, requiring large doses.

Complications of Beta Radiation

Cataracts.—Any opacity in the lens, with or without reduction in vision, is termed a cataract. With this definition, cataracts have been observed in both rabbits and humans after beta radiation from radium, radon, and Sr^{90} applicators.[6] Treatment over the limbus is most likely to produce lens opacities because the sensitive germinative cells at the equator of the lens are only 3 mm. away from the surface of the limbus, and from 4 to 18% of the surface dose from these applicators reaches this area.

In the study referred to previously,[4] no radiation cataracts were observed in any of the 192 patients treated for conditions of the lids. A total of 213 eyes, which had received beta radiation treatment to the globe, were examined to determine the presence or absence of radiational lens opacities. Of these, 45% had definite radiational opacities, and 12% had probable radiational opacities. The earliest cataracts were seen two and one-half years after treatment, larger doses producing opacities somewhat earlier than smaller doses. The smallest dose which produced equatorial vacuoles in the lens was 4 gram seconds when the radon applicator was used and 5,000 rad when the Sr^{90} applicator was used. On the other hand, other eyes showed no evidence of cataracts for as long as eight years after exposure to 12 gram seconds of radon or three years after exposure to 7,000 rad of strontium^{90}. Peripheral radiational vacuoles in the lens usually assumed a wedge-shaped configuration and, with larger doses of radiation, migrated posteriorly. Of the cases

observed both in 1953 and 1957, 79% showed progression of the opacities, 11% no progression, and 9% showed actual regression. Of 121 eyes with definite or probable radiational opacities, 19 previously treated with radon and 7 previously treated with Sr^{90} had opacities which reached the posterior pole of lens where they might have interfered with vision. Two beta radiation cataracts were extracted, and three additional cataracts were extracted from eyes which had received both x-ray and beta radiation.

Other Complications.—A year or more after administration of doses as low as 7,000 rad to the conjunctiva, telangiectases developed in and around the area of radiation. In one-third of these cases, these postradiational vessels created a real cosmetic blemish, especially when located within the palpebral fissure. Interference with wound healing was noted in approximately half of the 17 corneal transplantations and 10 cataract extractions performed on eyes which had been treated with beta radiation from six months to nine years prior to surgery. This confirms the previous experimental results in rabbits.[7] Since radiation is primarily destructive, the therapist must be careful to avoid accentuation of necrosis and ulceration already present. This is particularly true of acute chemical burns, corneal ulcers, and inflammatory processes.

Summary

Beta-radiation ophthalmic applicators, particularly the radioactive strontium (Sr^{90})-yttrium (Y^{90}) applicator, provide a ready source of radiotherapy for superficial lesions of the eyes. The general indications for beta radiation of the eye are the same as those for other forms of radiation such as x-ray. Because the therapeutic dosage and the dosage which might result in later complications are fairly close, exact knowledge must be obtained concerning the output of the applicator in rad per second, the depth dose, biological standardization, and the differential sensitivity of the tissues to be destroyed compared with the normal ocular tissues. This is particularly important when radiation is given over the region of the limbus which is only 3 mm. away from the sensitive equatorial region of the lens. Minimal cataractogenic doses appear, at this time, to be approximately 5,000 rad at the applicator surface with the Sr^{90} applicator when applied over the limbus. Minimal lens opacities in the periphery do not necessarily progress or affect vision, and certain serious ocular conditions requiring beta radiation warrant the necessary risk of producing a cataract later. In general, beta radiation should be reserved for use in those ocular conditions in which it is superior to other methods of treatment or in which other methods have failed.

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ACCIDENTS IN CHILDHOOD.—The death rates from accidents actually declined 42 per cent from 1928 to 1957. This decline is primarily due to improvement in the care of the victim and not the result of a decrease in the rate of accidental injury. During the same period, however, mortality from most other causes in childhood declined even more dramatically, leaving accidents as the most common serious health problem of childhood today. Home accidents account for 38 per cent of all accidental deaths in children under fifteen years of age, and in the age group under five, 58 percent of accidental deaths occur in or about the home.—R. J. Haggerty, M.D., Home Accidents in Childhood, *The New England Journal of Medicine*, June 25, 1959.

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PROBLEMS OF IMPAIRED SPEECH AND LANGUAGE

GUEST EDITORIAL

Wendell Johnson, Ph.D.

THE process of symbolization is the most distinctively human of man's bodily functions. The clinically recognized impairments of the symbolization process are primarily those of spoken language. Disorders of spoken language involve impaired phonation, speech sound articulation, fluency and rate, or symbolic representation, singly or in combination, associated or not with significant organic or physiological complications or emotional disturbance.

The clinically significant organic or physiological conditions most often associated with speech problems are those related to hearing loss, cleft palate, laryngectomy, cerebral palsy or other types of neuromuscular impairment, brain damage including cerebrovascular accident with attendant aphasia and dysarthria, and retarded or limited development affecting language and speech. Associated emotional reactions are rather more likely to be effects than causes of the speech disorder, and are, in any event, interactive with it.

The magnitude of the problem is suggested in part by current estimates of incidence. I recently had occasion to appraise relevant aspects of the situation for the United States Office of Education and concluded that probably 4% of all children enrolled in the public and private elementary and secondary schools of the United States have socially and educationally significant speech problems.[1] This amounts to a total of 1,600,000, assuming a national public and private school enrollment of 40 million. About 1 million of these children present faults of articulation, such as lisping, not associated with organic pathology. About 280,000 school children stutter, 200,000 have impaired speech associated with hearing loss, 40,000 have voice problems, and about 20,000 present each of the following faults: fluency and rate problems, retarded speech development, speech difficulties related to cleft palate and lip, and problems of speech and voice associated with cerebral palsy and other types of disturbed neuromuscular functioning.

Incidence data for adults are limited. There are, certainly, relatively more cases of functional misarticulation among children and more cases of aphasia and impaired speech and voice associated with laryngectomy and vocal cord pathology among adults. Stuttering affects from 6 to 8 per thousand children and college-age adults, but the incidence for more advanced age levels has not been well determined. Decreased auditory acuity and other effects of aging tend to be reflected in modified speech and language, with varying degrees of personal and social significance.

Present knowledge indicates that, by conservative estimate, there are probably 2,500,000 children and adults in the United States with speech, voice, and language impairments of relatively severe grade.[2]

The problems presented by these 2,500,000 persons are both medical and nonmedical, and they are most constructively managed through flexible patterns of multidisciplinary cooperation, varying with the needs of specific speakers. The medical specialists most often concerned with conditions functionally related to speech, voice, and language disorders are the otolaryngologists, oral surgeons, neurologists, neurosurgeons, orthopedic surgeons, psychiatrists, pediatricians, and general practitioners.

The nonmedical profession that has developed in response to the growing demand for educational and remedial services in this field is that of speech pathology and audiology, representing the speech and hearing sides of the coin of impaired communication.[3] This profession functions through the American Speech and Hearing Association (1001 Connecticut Ave. N. W., Washington 6, D. C.), which administers clinical certification for its members at basic and advanced levels in speech and hearing, respectively, publishes the *Journal of Speech and Hearing Disorders* and the *Journal of Speech and Hearing Research*, and seeks to improve the research and professional training programs and the educational and clinical services within its sphere of responsibility. Two-thirds of its roughly 5,000 members hold graduate degrees, and some members are physicians.

As a profession, speech pathology and audiology synthesizes the resources of several scholarly and scientific fields, particularly phonetics, semantics, psychology, psychoacoustics, genetics, anatomy, physiology, and neurology, as well as education, sociology, and cultural anthropology. Within the resultant interdisciplinary framework a growing body of research data, theory, and clinical technique has been accumulated. The number of uni-

From the Department of Speech Pathology and Audiology, State University of Iowa, Iowa City.

versities with departments of speech pathology and audiology and graduate programs in the field is gradually increasing. An estimated 1,000 to 1,200 graduates at all degree levels are being trained annually and an increasing refinement of the profession's standards of training parallels its growth. Other professions which contribute substantially to the effectiveness of services for persons with speech impairment are dentistry, particularly orthodontia and prosthodontia, education, and clinical psychology.

Speech correctionists do their work for the most part in two general settings: (*a*) the schools and (*b*) university and community speech and hearing clinics, hospitals, hospital-schools, rehabilitation centers, and institutions for the handicapped or retarded. So far as sheer number of cases is concerned, most speech correction is done in the public schools, primarily in the early grades. Most public school speech correction cases are those involving speech sound misarticulation without organic or severe emotional complications. Although school personnel commonly devote time to persons with organic speech problems and to those with complex emotional involvements, the services rendered tend to be demanding and extremely time-consuming. Moreover, they must be coordinated with essential medical and surgical measures, and as a consequence these more complex speech problems are generally dealt with wholly or in part in speech clinics outside the school.[4] Many universities conduct intensive summer speech clinics for school-age children.

Since speech correction is severely demanding of time and attention to detail,[5] and because of the nonmedical character of the required specialized training, it is the exceptional physician who is disposed to prepare himself by formal training to assume responsibility for speech correction, per se. Meanwhile, most physicians have a constant opportunity and ever-recurring obligation to consult with professional workers in speech pathology or to secure for their patients needed speech correction services. This is particularly true in patients requiring surgery that clearly or possibly will affect the speech function, as in cleft palate repair and laryngectomy. It is true as well in the development of an optimal rehabilitation program in any case of neuromuscular dysfunctioning involving the speech mechanism. Adequate treatment and care in cases of cerebrovascular accident necessarily include appropriate speech and language appraisal and indicated retraining procedures. Maximally effective treatment for patients with impaired hearing involves, as a matter of course, not only essential audiological measures with respect to hearing aids and auditory training but instruction and counseling designed to restore or preserve clear and well-modulated speech.

Pediatricians and general practitioners have frequent need to give counsel in response to parental concern over childhood speech—especially when such concern is not justified and is most likely, therefore, to have harmful effects. Little doubt remains that stuttering, for example, originates primarily in the disturbing perceptions and judgments of the listening parent responding with ill-informed preconceptions to the child's normally hesitant early attempts to negotiate the intricate neuromuscular and psychosocial complexities of spoken language.[6] We know now that the problem we call stuttering is not to be confused with the matter (it is seldom a problem) of speech nonfluency, per se.

Considerable research to date provides no appreciable support for the hypothesis that stuttering is characteristically associated with or symptomatic of severe emotional disturbance or neurosis in a clinically significant sense.[7] The counseling and retraining procedures needed by adolescent and adult stutterers, as well as by most persons with other types of impaired speech, appear to be, in their own way, of a piece with those required by the handicapped and mistutored rather than the neurotic or emotionally unstable.

The significance of the process of symbolization in relation to health and disease awaits the definitive scientific appraisal that its distinctively human character urgently warrants. Its role in the iatrogenic[8] and semantogenic[9] disorders would appear to be basic. It seems likely that it provides the major mechanism for psychosomatic reactions and for the patient's mode of adjustment to illness of whatever sort—and to wellness. The overriding consideration is that symbolization is a bodily process, mediated by the nervous system, and that it interacts necessarily with other bodily functions. There is little to be said for disregarding its gross disorders; there is much to recommend sophisticated attention to its seemingly minor but innumerable miscarriages.

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ORGANIZATION SECTION

STATEMENT TO SUBCOMMITTEE ON HEALTH AND SAFETY

July 6, 1959

Hon. Kenneth A. Roberts, Chairman
Subcommittee on Health and Safety
Committee on Interstate and Foreign Commerce
House of Representatives
Washington 25, D. C.

Dear Congressman Roberts:

This will acknowledge with thanks the notices dated June 18, 1959, addressed to me as Executive Vice President of the American Medical Association, and to Dr. Fletcher D. Woodward, the Chairman of our Committee on Medical Aspects of Automobile Injuries and Deaths. With your permission the Association would like to submit this statement for inclusion in the printed record of the hearings on the measures outlined in the notice of June 18.

Inasmuch as the American Medical Association has not considered or taken a position on most of the specific bills under consideration by your Committee, our statement will be general in nature. It will, however, I believe, outline the extent of our interest in this field and underscore our conviction that regulatory action at an early date is imperative.

The American Medical Association has been concerned with the problem of automobile injuries and deaths for many years. Actions of our House of Delegates on this subject are numerous and date back as far as 1929. In 1948, our House passed the following Resolution:

WHEREAS, The American Medical Association has in the past cooperated with the National Safety Council in its efforts to reduce the incidence of deaths and injuries from accidental causes; and

WHEREAS, The studies that have been made by the Bureau of Medical Economic Research of the American Medical Association have established the fact that fatal accidents cut off more years from the working lifetime of the American people than any one natural cause of death, and

WHEREAS, In the recent report made to the President by the administrator of the Federal Security Agency, it was stated that 40,000 deaths annually from accidents were preventable; therefore be it

Resolved, That the Board of Trustees be instructed to cooperate in every possible way with the National Safety Council and with every other agency, both public and private, concerned with accident prevention, to the end that research in accident prevention be further stimulated; that this excessive drain on hospital and medical facilities be lessened, and that the appalling loss of working years be reduced.

For more than 30 years our Association has had Committees actively working on the various aspects of the automobile accident problem. The present Committee, known as the Committee on Medical Aspects of Automobile Injuries and Deaths, was appointed by our Board of Trustees in 1955. Its members are chosen from physicians who by their interest and work are considered to be well qualified in this field.

We believe most people will agree that those who are called upon night and day to pronounce dead those persons killed on our highways, and who mend the broken bodies of those who are injured, can well be classified as interested and qualified in their efforts to prevent such carnage. Within the lifetime of most of us, we have seen substantial gains by the medical and allied health professions in the conquest of disease and disability. Many of the diseases that were commonplace early in this century have been conquered or brought under effective control. Many diseases that were once widespread are now a rarity. However, accidental injuries and disabilities due to automobile accidents have become the number one public health problem of our time. We believe it is important, therefore, that the medical profession continue to increase its interest in the automobile accident problem until effective improvement is a reality.

As the result of our studies, we are convinced that if speed, recklessness and drunken driving are controlled, and if improvements in automobile engineering are provided to protect those involved in collisions, then the present appalling toll of injuries can be substantially reduced. We are further convinced that enough facts are at hand to accomplish this purpose.

One of our most important objectives has been to provide the practicing physician with technical medical information which will enable him to advise and inform his patients relative to driving limitations that may be involved because of the effects of drugs or alcohol or the existence of physiological, pathological or emotional conditions.

We realize that a certain percentage of accidents are undoubtedly caused directly or indirectly by medical conditions, drugs, and other related physical factors. In an effort to identify these problems and to develop workable solutions, we sponsored a

symposium on Medical Aspects of Automobile Injuries and Deaths at the Association's Annual Meeting in June, 1956, in Chicago, and in June, 1958, in San Francisco. Papers presented at these meetings were published in THE JOURNAL of the American Medical Association on January 26, 1957, and April 4, 1959. Reprints are attached for you and for the members of your Committee.

Our next objective was to prepare a comprehensive book to serve as a guide to physicians in determining fitness to drive as related to the medical background of the individual. This book, a copy of which is attached, represents a compilation of medical data and the opinions of nationally recognized authorities in the various special fields of medical practice. With this information available, it should be possible for the individual physician to make a significant contribution to the welfare of his personal patients and the public at large.

Closely related to the need for factual information to aid the physician is the need to inform the driving public, through use of proper media, of the medical conditions which may affect their driving proficiency. We believe that many individuals would voluntarily discontinue or diminish radically their driving if they understood the dangerous possibilities involved in certain physical disorders and the potential effects of certain medications. In other words, we believe the technical information furnished the physician should be supplemented with a pamphlet written at the popular level and covering the more commonly encountered medical situations. In this way the patient can have the advantage of written information which will serve to instruct him as to whether he should or should not drive; and, if so, under what safeguards. Such a pamphlet, entitled "Are You Fit to Drive?" has been prepared by our Committee on Medical Aspects of Automobile Injuries and Deaths, in cooperation with the Center for Safety Education of New York University.

There is little doubt that a great deal of attention must be given to the very serious question of who shall be permitted to drive an automobile and who shall be denied that privilege. We emphasize that driving should be a privilege rather than a right. Therefore, our third objective is to develop better medical standards for driver licensing, including preparation of a guide for license examiners and assistance to state agencies concerned with licensing. This will be based on the information compiled in the medical criteria mentioned earlier and will constitute our recommendations for state licensing agencies. We recommend that each state medical society have a committee on traffic safety, with objectives such as those outlined on the attached green sheet. Such committees would be in a position to advise and assist state driver licensing bodies in the improvement of medical standards for licensing.

Another objective is to study and report on the design features of automobiles. Improvement of the design and safety equipment of automobiles promises the greatest possibility for rapid reduction in the automobile injury and death toll. If it is estimated that the average life of an automobile is ten years, it is apparent that a very considerable reduction in the severity of injuries and a marked reduction in fatalities could be accomplished in that time if more attention were devoted to providing safety rather than to increased horsepower, streamlining, color, and chrome.

The engineers and designers of the automobile—a relative handful of men in the industry—virtually control the destinies of the American public on the highways. They are the men who decide which elements of safety design will be put into or left out of next year's new automobile.

There is presently available an ample body of research data which clearly indicates the definite values of certain safety features of automobile design, construction and equipment. Yet, these safety features, if available at all, are all too often offered as optional equipment at extra cost. The automobile industry can make a great contribution toward solution of this problem by consulting with physicians, anthropologists, psychologists, related biological scientists, and other scientific professions, and by giving realistic consideration to the wide range of physical characteristics of automobile drivers and riders and what happens to them in a collision.

In the past the automobile industry has made many important contributions to safety. However, in recent years, safety has generally been ignored in favor of other developments. The following suggestions have been repeatedly advanced by physicians, researchers, and safety engineers with but little success:

1. Anchorage for seat belts should be standard equipment. The public also needs education in the value of seat belts. The only evidence so far presented against seat belts is in the number of deaths in sports cars during roll-overs. This is not an argument against seat belts but against the design of such cars which do not provide roll-over bars. It should be quite simple to incorporate such a bar in the windshield and a second one back of the seat.
2. Crash padding of the dash, roof, and other areas should be provided.
3. An improved steering wheel and recessed post; perhaps a collapsible assembly.
4. Safety door locks should be standard in all cars.
5. Removal of dangerous knobs, buttons, sharp edges, and other gadgets.
6. Seats should be securely anchored to the floor of the car and should be locked into position. They should also be high enough in the center to protect the neck in a rear-end impact and prevent neck-snap injury (also called whiplash).

7. Eliminate the deck behind the rear seat as a storage place for flying missiles or provide it with an effective retaining rail or construct it as a recessed pocket.
8. Eliminate sharp, pointed hood ornaments. These fill no functional need and are potentially lethal to pedestrians.
9. Eliminate other hazardous exterior design features such as sharp, pointed bumper ornaments.

In addition, we feel that the automobile industry should make an open-minded examination of other suggestions and adopt them where feasible. For example:

1. Shock-absorbing bumpers: if one drives his car into a brick wall at one mile per hour, he will be astounded at the shock transmitted by such an impact. One person testifying last year intimated that to absorb the energy at 20 miles per hour in a 4,000-pound car, such a bumper would have to be 16 feet long.
2. Polarized headlight lenses and an oppositely polarized windshield spot. They would prevent glare at night and thereby prevent many pedestrian accidents and deaths.
3. Consideration should be given to the design of windshield and rear windows to meet standards based on optical principles.
4. Provide protective side-swipe bumpers along the sides.
5. Provide warning reflectors on the sides.
6. Remove tail lights from the realm of the artistic designer.
7. Provide a positive separation of turn signal lights from other lights.
8. Eliminate the glare-reflecting surfaces on the interior.
9. Provide accurate speedometers. Why do we have speedometer dials indicating up to 120 miles per hour? Why not an audible warning device to denote when safe speed has been passed?
10. Construct drivers' seats with better regard for the posture and visibility of persons of various heights.
11. Make chrome, clocks, radiator ornaments and other expensive gadgets optional equipment and install safety equipment as standard equipment.

The following Resolution adopted by the House of Delegates of the American Medical Association at its meeting in Boston on December 1, 1955, is evidence of the interest in this subject by the entire medical profession and the conviction that something constructive can and should be done toward the prevention of injuries:

WHEREAS, Traffic accidents in the United States claim 38,000 lives and 1,250,000 injured each year, with a probable 45% increase in vehicle mileage in the next ten years; and

WHEREAS, This death and accident toll could be materially reduced through improvement in automotive safety design and construction; and

WHEREAS, All other modes of public transportation except automobile are already safeguarded by Federal safety standards; therefore be it

Resolved, That the American Medical Association, through its House of Delegates, strongly urges the President of the United States to request legislation from Congress authorizing the appointment of a national body to approve and regulate safety standards of automobile construction.

On January 9, 1956, Dr. George F. Lull, who was at that time Secretary and General Manager of the Association, addressed a letter to President Eisenhower in which he directed attention to the Resolution.

Another objective of the Association is to promote the extension of emergency first aid training to as many citizens as possible. This training will be of value not only in connection with the reduction of the severity of automobile crash injuries, but also in connection with civil defense needs as well. We feel it is also desirable, therefore, that all automobiles be equipped with first aid kits.

Related to first aid is another objective—to assist in the promulgation and to promote the use of standards for organized emergency services in local communities, including training of rescue squads and standardized equipment for rescue vehicles. This is a future activity in which we will work through state and county medical societies. An example of one problem in this area is the need for better selection, education and control of drivers of emergency vehicles.

As citizens and physicians, we recognize the importance of driving courses for all high school students. Similar courses should be provided for the public and the curriculum should meet certain basic educational requirements. We sincerely hope the day will soon come when such certificates will be required of all prospective drivers as well as for repeat traffic law violators.

Since speed and driving under the influence of alcohol and their related offenses are intimately associated, we feel that strict legislation in this field should be provided. The public needs to be aroused to the point whereby the legislators will provide these laws and the traffic courts will administer them without fear and with complete impartiality.

Because of the indefatigable work of many safety organizations over the years, the incidence of death has been greatly reduced in spite of the tremendous increase in the number of vehicles and number of miles traveled. In spite of this apparent success as to the incidence rate, the total number of deaths

and injuries is increasing each year. Unless some of the suggestions mentioned above are followed, it seems inevitable that this number will continue to increase despite the splendid work now being done.

Your willingness to permit the American Medical Association to present its views with respect to the legislative proposals under consideration by your Committee is sincerely appreciated.

Sincerely yours,
F. J. L. BLASINGAME, M.D.
Executive Vice-President

STATEMENT OF DR. GEORGE M. FISTER ON H. R. 10, BEFORE FINANCE COMMITTEE OF SENATE

Mr. Chairman and Members of the Committee:

I am Dr. George M. Fister of Ogden, Utah, where I am engaged in the private practice of medicine. I am a member of the Board of Trustees and the Chairman of the Council on Legislative Activities of the American Medical Association. With me is Dr. Vincent W. Archer of Charlottesville, Virginia, a member of the American Medical Association's House of Delegates and a member of our Committee on Federal Medical Services.

We are here today as representatives of the American Medical Association to express the wholehearted support of the medical profession for H. R. 10, 86th Congress, a bill which, if enacted, would provide a measure of tax equity for the self-employed including physicians in private practice.

I shall not review or attempt to summarize the provisions of the pending bill since I am sure that you are all completely familiar with the measure. I would like to restate very briefly, however, the history of the support of legislation of this type by the American Medical Association.

In 1948 our Board of Trustees was apprised of a movement to encourage the enactment of Federal legislation which would enable self-employed persons, including physicians, to provide for their own retirement benefits through the payment of amounts annually from their taxable income to finance retirement plans. The Board approved this movement, suggesting that there be a reasonable limitation on such retirement benefits. This action was endorsed by our House of Delegates, the governing body of the Association, at its meeting in June, 1948.

In June, 1951, at the annual session of the American Medical Association, three resolutions emphasizing our endorsement of this principle were adopted by the House of Delegates. On numerous occasions since that time the House has reiterated this endorsement and has recommended that each member of the Association give the matter his careful study and active support.

In the 82nd, 83rd, 84th and 85th Congresses, the Association, through its representatives, expressed support of this type of legislation before the Ways and Means Committee of the House of Representatives. A similar expression of support was communicated by letter to that Committee earlier this year. We have also collaborated closely with representatives of the American Bar Association, the original sponsors of this measure, and other national organizations of self-employed taxpayers who would be covered by the provisions of the bill.

It is the belief of the American Medical Association that physicians, dentists, farmers, lawyers, architects, veterinarians, merchants, and the many others who comprise the nation's self-employed have long been neglected in Federal tax legislation relating to pensions. Under existing law, corporations are entitled to set aside tax-free money to purchase pensions and annuities for their employees, and millions of employees are benefiting from that arrangement. With high taxes and inflated living costs, it is difficult for the self-employed person to set aside adequate funds for retirement without a tax deferment similar to that available to corporate employees. The purpose of this bill is to eliminate this discrimination and inequity. By extending the tax deferment privilege to the country's eleven million self-employed, this legislation will give them an opportunity during their best earning years to save for their old age.

Unless something is done to make self-employment as financially attractive as employee status, we believe that there is a real danger that many professional men will bypass the private practice of their profession. A shift away from individual enterprise has become noticeable in the past few years. A continuation of this situation may not only limit individual initiative but may also create a shortage of medical services in certain areas. For example, it could contribute to a maldistribution of physicians since it makes the large city more attractive to the young professional man by providing more opportunities for him to become employed. I am convinced that the enactment of this legislation would make the smaller communities of America better able to compete with the big cities for the services of physicians.

On the basis of my own observations over many years of practice in medicine, I am convinced that this is one of the factors contributing to the pronounced migration of professional people into urban areas. So, quite apart from the objective of obtaining tax equality with our employed counterparts, we urge you to approve legislation of this type, because it is in the public interest.

This legislation will be of particular benefit to physicians and other professional men who go through a long and costly period of training, and whose earnings are received in a comparatively short period of years when they are subject to high income tax rates.

Under the program proposed in the pending bill, the amount of each person's pension would be determined by his own contributions, without any funds being added by the government. In addition, the program would have the advantage of not forcing an individual into idle retirement in order to draw upon his pension fund. Most important, it presents an opportunity for the self-employed to provide for their own retirement without undue discrimination.

Because such a law will remove the existent discrimination against the self-employed citizen, the American Medical Association strongly urges its favorable consideration by your Committee.

Mr. Chairman, let me take this opportunity to thank you and the Committee for allowing us to express the views of the American Medical Association on this important measure. Dr. Archer and I will be happy to answer any questions the Committee may have.

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DR. BRAMLITT TO BE SECRETARY OF COUNCIL ON SCIENTIFIC ASSEMBLY

Dr. Charles H. Bramlitt, recently retired from the U. S. Air Force and currently Secretary of the Section on Military Medicine of the Scientific Assembly of the American Medical Association, will become a member of the staff of the American Medical Association on Aug. 1 and will work with Dr. Hull. When Dr. Hull retires as Secretary of the Council on Scientific Assembly at the end of the year Dr. Bramlitt will become Secretary.

CHANGE OF ADDRESS

If you change your address please notify THE JOURNAL at least six weeks before the change is made. Include the address label clipped from your latest copy of THE JOURNAL, being sure to clearly state both your old and new address. If your city has Postal Zone Numbers, be sure to include this Zone Number in your new address.

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MEDICAL NEWS

CALIFORNIA

Ophthalmologist Honored.—A special number of the *American Journal of Ophthalmology* has been dedicated to Dr. Frederick C. Cordes, San Francisco, chairman, department of ophthalmology, University of California School of Medicine. This issue was dedicated to Dr. Cordes on the occasion of his 67th birthday and his retirement from the faculty. He has been department chairman since 1934 and a member of the U. C. Medical Center staff since earning his M.D. degree there in 1918. The issue contains tributes to Dr. Cordes' accomplishments in medical education and the study of eye diseases by several distinguished ophthalmologists and by associates in the university, including President Emeritus Robert Gordon Sproul.

Personal.—Dr. James N. Waggoner, Chicago, regional medical director for United Air Lines, has joined the Garrett Corporation's AiResearch Manufacturing Division of Los Angeles as medical director.—Dr. Howard R. Bierman resigned as director, Hospital for Blood Diseases and Medical Oncology, and scientific director, City of Hope National Medical Center, Duarte, to enter practice as a consultant in neoplastic diseases, the leukemias, and blood dyscrasias. He is establishing practice in Beverly Hills and will continue his research program. He will continue as a consultant to the City of Hope, with which he had been associated since 1953.

CONNECTICUT

University News.—Dr. Paul Howard-Flanders, of London, England, was appointed associate professor of radiology, Yale School of Medicine, New Haven. Dr. Howard-Flanders served as a lecturer in biophysics at the University of California in 1957-1958. At Yale he will conduct research in fundamental problems concerning the effect of ionizing radiation on biological systems.—Dr. Edith B. Jackson, child psychiatrist at the Yale School of Medicine, is retiring this summer after more than 25 years on the faculty. Dr. Jackson was director of the "rooming-in" project at the Yale-New Haven Medical Center from 1946 to 1951. In honor of her retirement, her colleagues and friends have given to Yale a portrait of Dr. Jackson, which will hang in the Grover F. Powers Pediatric Study of the Medical Center.

Physicians are invited to send to this department items of news of general interest, for example, those relating to society activities, new hospitals, education, and public health. Programs should be received at least three weeks before the date of meeting.

FLORIDA

International Dermatology Symposium.—An International Symposium on Griseofulvin and Dermatomycoses will be held at the University of Miami School of Medicine, Oct. 26-27. Under the sponsorship of the medical school's department of medicine, 50 American and foreign authorities will discuss the mechanism of action of Griseofulvin, its experimental toxicology, and its use in fungous diseases of the hair, skin, and nails. Among those scheduled to give papers are Dr. A. Kaminsky, Buenos Aires Medical School; Dr. F. Latapi, Medical School of Mexico City; Dr. S. C. Desai, Medical College of Bombay; and Dr. R. S. C. Aytoun and Dr. A. H. Campbell, of Glaxo Laboratories (England). The use of Griseofulvin in onychomycosis, tinea pedis and capitis, favus, endothrix *Trichophyton* infections, and deep mycoses will be discussed, as well as laboratory, animal, and experimental studies on the drug. Information may be obtained from Dr. Harvey Blank, professor of dermatology, University of Miami School of Medicine, Miami, Fla.

State Residency Required for Miami School.—The University of Miami School of Medicine, which has previously required a seven-year residence in Florida for admission to its classes, will, beginning Aug. 6, admit students if they have legal residence in the state. This period has been set at one year by the state authorities. The law affecting the admission of students to the medical school here was changed by the State Legislature at the recent session, it was announced by Dr. Homer F. Marsh, dean of the school. By the terms of the subsidy granted to the school by the State of Florida, 90% of the student body must be residents of the state. The definition of residence has been modified so that the medical school admission requirement is now the same as that for the universities operated by the state itself. The medical school has for the past two years admitted five out-of-state residents and about 70 Floridians to each freshman class. Prior to 1957 no out-of-state applicants were admitted. The medical school, opened in 1952, graduated its first class in 1956 and now has 178 alumni. The freshman class to be admitted in September will number about 75 students. Total number of students in the school now is 270.

ILLINOIS

Mental Hospital Addition.—A preview open-house and tour of a new, 30-bed, $150,000 addition to Forest Hospital, a private mental institution, was

held Aug. 8 at the hospital, 555 Wilson Lane, Des Plaines. The tour included all the features of the 6,000 square foot addition, such as the solarium, patients' rooms, treatment and consultation rooms, nurses' rooms, and staff offices. Furnishings in the new private, double, and three-bed rooms include sofa beds, desks, lounge chairs, and original paintings to produce the appearance of lounges, rather than of hospital rooms. The present facilities of 50 beds will be increased to 90 with the new addition.

Chicago

Lecture by Uruguayan Physiologist.—Prof. Roberto Caldeyro-Barcia, chairman, section on obstetrical physiology, School of Medicine, Montevideo, Uruguay, will present "Recent Advances in our Knowledge on Oxytocin," Wednesday, Sept. 23, 4:30 p. m., at Dora De Lee Hall, The Chicago Lying-in Hospital, University of Chicago School of Medicine.

Dr. Newman Cited.—Dr. Louis B. Newman was the recipient of the 1959 "Citation for Public Service" from the University of Chicago. He was awarded the citation for having "accepted the privileges of a university education by assuming the obligations to society in exercising leadership in those civic, social, and religious activities that are essential to a democracy; for his public spirited citizenship and unselfish and effective service to the community, the nation, and humanity; and for the credit this service has reflected on the University and its alumni." Dr. Newman, chief of the physical medicine and rehabilitation service, Veterans Administration Research Hospital, is president of the American Academy of Physical Medicine and Rehabilitation.

INDIANA

Experimental Education Program.—Indiana University announced the appointment of Dr. Douglas A. MacFadyen, of the University of Illinois College of Medicine, Chicago, to direct its new experimental program in medical education to be inaugurated in September. The new program, "a departure and extension of traditional medical training," was announced early this year coincident with the university's receipt of a pilot grant of $173,000 by the Commonwealth Fund. Starting this fall with a limit of 10 students, selected from about 180 to be admitted to the School of Medicine, the program will draw on the resources of the College of Arts and Sciences and Graduate School and will be administered by the Medical School at Indianapolis under Dean John D. VanNuys. Eventually, 30 students at the end of their junior year in arts and sciences will be selected. "Students in the new program," it was explained by Dr. MacFadyen, "will accomplish work for an A.B. degree and then work in the six preclinical departments constituting the first two years of a medical curriculum and a broader than usual scientific and cultural training capped by an A.M. degree. Thereafter, each student may proceed in either of two directions, either to a medical career after a clinical training with or without further work in the Graduate School or to some other career in research and teaching." The new program has these objectives: a thorough training in polytechnical and cultural subjects, preparation of medical students whose paramount interests are in research and teaching, and an increase in the number of "broadly qualified" physicians. Dr. MacFadyen, also will be professor of pathology in the School of Medicine.

NEW JERSEY

Change of Address.—The new address of the Academy of Medicine of New Jersey is: Academy of Medicine of New Jersey, Library, 307-17 Belleville Ave., Bloomfield, N. J. The old address, no longer effective, was 91 Lincoln Park, Newark 2, N. J.

Survey of Nurses.—Rutgers University College of Nursing, in cooperation with the New Jersey Division of Civil Defense, will distribute a questionnaire in October to the state's 35,000 registered professional nurses to inventory their qualifications and locations and note shortages. The four-page survey has 46 questions. The study seeks to determine where nurses are employed, type of nursing performed, educational qualifications, psychiatric and public health nursing education and experience, degree of activity and income during 1959, specialized experience, postlicensing education and reasons for inactivity in the profession.

NEW YORK

New York City

Personal.—Dr. Irwin L. V. Norman was appointed medical director of The Chase Manhattan Bank. Dr. Norman served in the U. S. Navy from 1927 until April 30, when he retired with rank of rear admiral.——Dr. George M. Wheatley was appointed head of the Metropolitan Life Insurance Company's health and welfare division, succeeding Dr. William P. Shepard, who recently was appointed chief medical director of Metropolitan and placed in charge of all the company's medical and public health activities.

Dr. Ferree Named Director of Blindness Society.—Appointment of Dr. John W. Ferree as successor to Dr. Franklin M. Foote, former executive director of the National Society for the Prevention of Blindness, was announced by Ira V. Hiscock, Sc.D., the Society's president. For the past 11 years Dr. Ferree has been director of Community Service and Education and for two years associate medical director of the American Heart Association. Dr. Foote resigned recently to accept appointment as commissioner of the Connecticut State Department of Health, Hartford. The Connecticut health pro-

gram is being expanded to include administration of four hospitals for chronic disease and two for mentally handicapped children.

Dr. Swan Named Anatomy Chairman.—The appointment of Dr. Roy Craig Swan Jr. as chairman of the department of anatomy has been announced by Cornell University Medical College. Dr. Swan from 1950-1952 was a research fellow in medicine, Harvard Medical School, and resident in medicine, Peter Bent Brigham Hospital, Boston. Since then he was an instructor, assistant, and then associate professor of physiology at Cornell University Medical College. He has been a Life Insurance Medical Research Fund Fellow and a Markle Scholar in Medical Sciences. He is a diplomate of the American Board of Internal Medicine.

Units for Heart Disease Patients.—Two new units of a program to advance Presbyterian Hospital's facilities for the diagnosis and surgical treatment of heart diseases have been completed. The program was facilitated by a research grant from the John A. Hartford Foundation, Inc., and is the result of three years planning by a group of Columbia–Presbyterian Medical Center anesthesiologists, surgeons, cardiologists, and radiologists. The cardiac special care unit is a recovery room for patients who have undergone heart surgery. The unit is staffed by nurses with experience in the postoperative care of this type of patient and fills the need of providing intensive care over a period of several days. Each of the five beds has its own battery of equipment for constant monitoring of the patient's recovery. The diagnostic unit includes a modern angiocardiography room which will more than double Presbyterian Hospital's facilities for caring for cardiac patients.

OKLAHOMA

Doctors Building Opened.—The new seven-story Doctors Building at 21st and Lewis Streets, in Tulsa, was opened in June. Erected at a cost of $1,500,000, the structure provides offices for 53 physicians and four dentists. Among the facilities in the new building are two radiology laboratories, three pathology and bacteriology laboratories, a pharmacy, optician, and coffee shop. Work on the 65,000 square foot unit which was begun 15 months ago was financed by its tenants through the self-owned Twenty-first Street Building Corporation. The building has walls of insulated procelain steel panels, with structural columns and windows covered with aluminum. It is completely air-conditioned and uses a specially engineered type of heating equipment to meet the needs of multiple examination and treatment rooms. Each suite is designed to the individual requirements of the tenant. A parking area east of the building provides parking for patients and visitors. A second lot located west, across Lewis Avenue accommodates cars of doctors and office personnel.

Dr. Turner Named Schering Scholar.—The Endocrine Society named Dr. Henry H. Turner, Oklahoma City, as this year's Schering Scholar. The award was presented to Doctor Turner during June 5 ceremonies held in conjunction with the annual meeting of the organization in Atlantic City. An anonymous committee of the Council of the society selected Dr. Turner for the $2,500 grant on the basis of his accomplishments as an established investigator in the fields of endocrinology. The cash award is made possible by the Schering Corporation and is presented annually to a "deserving physician who wishes to extend the opportunities for his work either here or abroad." Dr. Turner has announced that he intends to utilize the grant by attending both the 1960 International Goiter Conference, London, and the International Congress of Endocrinology, to be held in Copenhagen the same year. While abroad, he will also visit with a number of European investigators. In addition to being the Schering Scholar, he holds the office of secretary-treasurer for the national organization and is president of the National Society of Nuclear Medicine.

OREGON

Meeting on General Practice in Portland.—The Oregon Academy of General Practice will present "Horse and Buggy Doctor" as the 12th annual scientific session of the Northwest Regional Academy meeting, Sept. 9-11, at the Portland State College, Portland. Dr. Howard A. Rusk, chairman, department of physical medicine and rehabilitation, New York University–Bellevue Medical Center, and Dr. Edward H. Rynearson, chairman, section on metabolic diseases, Mayo Clinic, Rochester, Minn., will be the Sommer Memorial Lecturers. Other speakers include the following: Drs. A. Cannon Eley, Boston; L. Henry Garland, San Francisco; Ian MacDonald, Los Angeles; John O. McCall Jr., Portland; Leland S. McKittrick, Brookline, Mass.; Frank W. Norman, Santa Rosa, Calif.; Richard H. Overholt, Boston; Robert H. Tinker, Portland; and Roger H. L. Wilson, San Francisco. At the annual banquet Sept. 10, 7:30 p. m., Dr. Fount Richardson, Fayetteville, Ark., president, American Academy of General Practice, will be the speaker. Exhibits are planned, and entertainment includes a cruise and deep-sea fishing. The program has been approved for 15 hours of category I credit. There is no registration fee. The theme "Horse and Buggy Doctor," was selected to celebrate Oregon's 100th birthday as a state. For information write Mrs. Thomas Sterm, Chairman, Advance Registration Committee, Route 4, Sherwood, Ore.

PENNSYLVANIA

Philadelphia

Dr. Koprowski Awarded Alvarenga Prize.—On July 14, the College of Physicians of Philadelphia awarded the Alvarenga Prize for 1959 to Dr. Hilary Koprowski, professor of research medicine, University of Pennsylvania, "for his outstanding work on the development of a living attenuated virus vaccine against poliomyelitis." The Alvarenga Prize was established by the will of Pedro Francisco DuCosta Alvarenga, of Lisbon, Portugal, an associate fellow of the College of Physicians of Philadelphia, to be awarded annually by the college on the anniversary of the death of the testator, July 14, 1883.

Personal.—At the 60th annual meeting of the American Gastroenterological Association Dr. Russell S. Boles was presented with the Julius Friedenwald Medal, awarded each year to a member of the association "for outstanding achievement in gastroenterology." —Dr. Gordon N. French, of Brookline, Mass., was appointed director of internal medicine at Misericordia Hospital. Dr. French was formerly on the faculty of medicine at Tufts University Medical School and a research associate in physiology at Harvard School of Public Health.

Teaching and Research Center.—The development of a new integrated teaching and research center for the basic biological sciences at the University of Pennsylvania, to be closely associated with the university's School of Medicine, was made possible by three grants totaling $1,903,345. Grants of $1,000,000 from the Longwood Foundation, a philanthropic organization created by Pierre S. duPont; $473,345 from the U. S. Public Health Service; and $430,000 from the Rockefeller Foundation will bring into being a new building for the university's division of biology, directed by David R. Goddard, Ph.D., Gustave C. Kuemmerle Professor of Botany. Several levels will interconnect with the Medical School's research building. The grants also make possible rehabilitation of portions of an existing zoology building, to which the new structure will be joined, and provide construction of greenhouses and a service laboratory. The building will be adjacent to the School of Medicine's new medical research building under construction on Hamilton Walk. The new air-conditioned biology building will be about 36,000 square feet in area and will include lecture and seminar rooms, a biological library, teaching laboratories, and research rooms. The new 4,000-square-foot service laboratory, which will connect with the remodeled zoology building, will contain air-conditioned animal quarters and climatically and atmospherically controlled experimental plant growth chambers. Construction of the biology building, renovation of the zoology building, and construction of the adjacent structures will accomplish the university's goal of physical integration of the division of biology. The division was organized in 1957 through academic and administrative integration of the earlier departments of botany, zoology, and microbiology of the College of Arts and Sciences.

SOUTH CAROLINA

Hospital Dedicated in Charleston.—Dedication ceremonies for the new McClennan–Banks Memorial Hospital on Courtenay Drive, Charleston, were held on May 31. The 31-bed hospital, which cost $686,000 in county and federal funds, is now open for patients. It has one private room, 11 two-bed rooms, and two four-bed wards and a conference room. Dr. Thomas C. McFall, administrator of the new hospital, has been a leader in efforts to establish a new unit as a replacement for the old Negro Hospital and Training School on Cannon Street. The hospital is named in honor of Dr. Alonzo Clifton McClennan and Mrs. Anna D. Banks. Dr. McClennan helped found the old Negro center and served as its medical director and surgeon until his death in 1912. He was a native of Columbia and a graduate of Howard University schools of pharmacy and medicine. Mrs. Banks was the first head nurse of the old Hospital and Training School and later became superintendent of nurses. She died in 1930.

TEXAS

Dr. May Owen Honored.—Dr. May Owen of Fort Worth, Texas, was elected president-elect of the Texas Medical Association. She will be the first woman to hold the office of president in the association's 106-year history. Dr. Owen was the first woman president of the Tarrant County Medical Society and is a past-president of the Texas Society of Pathologists.

UTAH

Annual Scientific Session.—The 64th annual scientific session of the Utah State Medical Association will be held Sept. 16-18 at the Hotel Utah Motor Lodge, Salt Lake City. Dr. Ulrich R. Bryner, Salt Lake City, president of the association will open the session with an address. Two symposiums are planned: "Newer Adrenocorticosteroids," moderated by Dr. Frank H. Tyler, and "Basic Principles and Care of Hand Injuries," moderated by Dr. Thomas R. Broadbent. The program will include papers by the following out-of-state speakers: Drs. Edward L. Bortz, Philadelphia; Thomas McPherson Brown, Washington, D. C.; Charles R. Stephen, Durham, N. C.; James R. Willson, Philadelphia; Phillips Thygeson, San Jose, Calif.; James W. Littler, New York City; John L. Emmett, Rochester, Minn.; and Reginald H. Smithwick, Boston. An informal panel discussion moderated by Dr. John F. Waldo, president, Salt Lake County Medical Society, is planned for the luncheon of Sept. 16. Specialty group dis-

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cussions will be held the evening of Sept. 17. Dr. Louis M. Orr, Orlando, Fla., President, American Medical Association, will be the speaker at the president's banquet, 7:30 p. m., Sept. 18, presenting, "Medicine Is Not Failing America." For information write Mr. H. Bowman, 42 S. 5th East, Salt Lake City, Executive-Secretary.

WASHINGTON

Annual Convention in Seattle.—The 70th annual session of the Washington State Medical Association will be held Sept. 13-16, at the Olympic Hotel, Seattle. Dr. E. Vincent Askey, Los Angeles, President-Elect, American Medical Association, will be the featured speaker in the nonscientific program of the convention. Guest scientific speakers are: Drs. Lawson Wilkins, Baltimore; Carleton Mathewson Jr., San Francisco; John Shea, Memphis, Tenn.; Robert H. Williams, Seattle; and Frank C. Winter, Palo Alto, Calif. There will be Monday and Tuesday morning sessions with special subject matter in the following fields: pediatrics; internal medicine; ear, nose, and throat; surgery; and eye. General scientific sessions will be held in the afternoon. The scientific program will climax with a general scientific session the morning of Sept. 16 and a limited attendance seminar, "Electrolyte and Fluid Management Problems." President of the association is Dr. Emmett L. Calhoun of Aberdeen. For information, write Mr. Ralph W. Neill, 1309 Seventh Ave., Seattle 1, Executive Secretary.

GENERAL

Psychosomatic Meeting in Cleveland.—The sixth annual meeting of the Academy of Psychosomatic Medicine will be held Oct. 15-17, at the Sheraton-Cleveland Hotel, Cleveland. The meeting will be oriented and directed to fit the needs of nonpsychiatric physicians. Practical everyday office management of psychosomatic problems and emotional disturbances will be dealt with in formal papers, symposiums, panel discussions, and small study groups. The meeting will be open to all scientific disciplines, as well as psychologists, social workers, and nurses. Information may be obtained from Dr. Bertram B. Moss, Suite 1035, 55 E. Washington St., Chicago 2.

Society News.—At the 70th annual meeting of the **American Dermatological Association, Inc.**, in Atlantic City, Dr. Marion B. Sulzberger, of New York City, was elected president for the coming year, and Dr. Lawrence G. Beinhauer, of Pittsburgh, vice-president. Dr. Carl T. Nelson, of New York City, is treasurer, and Dr. Wiley M. Sams of Miami, Fla., secretary. The next annual meeting of the association will be held at the Boca Raton Hotel and Club, Boca Raton, Fla., April 8-12, 1960. ——The officers of the **American Proctologic Society** for the year 1959-1960 are: president, Dr. Hyrum R. Reichman, Salt Lake City; president-elect, Dr. Walter A. Fansler, Minneapolis; vice-president, Dr. Neil W. Swinton, Boston; secretary, Dr. Norman D. Nigro, Detroit; and treasurer, Dr. Robert J. Rowe, Dallas, Texas. The next annual meeting will be held April 25-27, 1960, at the Shamrock Hilton Hotel in Houston, Texas.

Mississippi Valley Meeting.—The 24th annual meeting of the Mississippi Valley Medical Society will be held at the Chase Hotel, St. Louis, Sept. 29-Oct. 1, under the presidency of Dr. Arthur F. Fritchen, of Decorah, Iowa. The morning and afternoon sessions on Sept. 29 will be devoted to clinics held in the teaching hospitals of St. Louis and Washington University schools of medicine. A joint meeting with the St. Louis Academy of General Practice and the St. Louis Dental Society will be held the evening of Sept. 29, with the opening of the industrial and scientific exhibits at 6:00 p. m. on that day. Over 30 clinical teachers are on the program. In addition, the program includes Dr. Jacob A. Bargen, Rochester, Minn.; Dr. Lester R. Dragstedt, Chicago; Dr. E. Grey Dimond, Kansas City, Kan.; Dr. J. P. Greenhill, Chicago; Dr. Heyworth N. Sanford, Chicago; and Dr. Robert L. Jackson, Columbia, Mo.; Dr. Harvey Flack of London, England, will be the banquet speaker. There will be panel discussions on pediatric heart problems, surgery in peptic ulcer, heart disease and atherosclerosis, and highway injuries. A complete program may be obtained from Dr. Harold Swanberg, Secretary, W.C.U. Bldg., Quincy, Ill. (The meeting will be followed by the 16th annual meeting of the American Medical Writers' Association at the Chase Hotel, Oct. 2-3.)

Rocky Mountain Medical Conference.—On Sept. 8-11, at the Shirley-Savoy Hotel, Denver, the 10th biennial Rocky Mountain Medical Conference will be held in combination with the 89th annual session of the Colorado State Medical Society. The conference is a joint enterprise of the Colorado, Montana, New Mexico, Utah, and Wyoming state medical societies. Guest speakers at the conference are as follows: Drs. Edward L. Bortz, Philadelphia; Harold W. Dargeon, New York; Fred C. D. Collier, Birmingham, Ala.; M. Edward Davis, Chicago; L. Henry Garland, San Francisco; L. Stanley James, New York; Theodore G. Klumpp, New York; Ben M. Peckham, Madison, Wis.; Jack Weinberg, Chicago; and Danely P. Slaughter, Chicago. Three closed circuit television clinics are planned: "Ob-Gyn and Pediatrics," "Leukemias and Lymphomas," and "Care and Rehabilitation of the Older Patient." Scientific and technical exhibits are planned. A program of entertainment and special events is arranged. A banquet will be held Sept. 10, at 7:30 p. m. Registration fee is $5. For information write Mr. Harvey T. Sethman, Executive Secretary, Colorado State Medical Society, 835 Republic Building, Denver 2.

Prevalence of Poliomyelitis.—According to the National Office of Vital Statistics, the following number of reported cases of poliomyelitis occurred in the United States, its territories and possessions in the weeks ended as indicated:

Area	July 25, 1959 Paralytic Type	July 25, 1959 Total Cases	July 26, 1958 Total
New England States			
Maine	..	..	..
New Hampshire	..	..	..
Vermont	..	..	..
Massachusetts	2	3	1
Rhode Island	..	..	..
Connecticut	1	1	..
Middle Atlantic States			
New York	7	7	6
New Jersey	2	2	10
Pennsylvania	7	9	4
East North Central States			
Ohio	4	9	8
Indiana	4	7	6
Illinois	2	6	3
Michigan	1	5	4
Wisconsin	..	1	1
West North Central States			
Minnesota	3	5	..
Iowa	6	20	..
Missouri	14	16	..
North Dakota	..	..	..
South Dakota	..	..	..
Nebraska	5	8	1
Kansas	2	8	1
South Atlantic States			
Delaware	1	1	1
Maryland	..	..	..
District of Columbia	..	..	1
Virginia	8	9	8
West Virginia	3	3	4
North Carolina	8	11	4
South Carolina	..	2	4
Georgia	1	1	1
Florida	5	8	3
East South Central States			
Kentucky	..	..	..
Tennessee	11	13	..
Alabama	20	24	1
Mississippi	1	2	3
West South Central States			
Arkansas	10	13	..
Louisiana	10	13	5
Oklahoma	5	8	4
Texas	15	31	28
Mountain States			
Montana	..	1	4
Idaho	..	1	1
Wyoming	..	..	..
Colorado	..	..	..
New Mexico	1	1	..
Arizona	1	3	..
Utah	..	..	2
Nevada	1	1	..
Pacific States			
Washington	..	1	2
Oregon	4	5	..
California	11	13	9
Alaska	1	1	..
Hawaii	..	..	2
Territories and Possessions			
Puerto Rico	..	..	1
Total	177	278	126

Care of Child with Rheumatic Fever.—A new booklet, "Home Care of the Child with Rheumatic Fever," was published by the American Heart Association and its affiliates. The booklet was prepared especially for parents of children who have rheumatic fever or are recovering from it and for whom hospital care is either not advised or not available. Copies may be requested by physicians and others from local heart associations to give to parents of rheumatic fever patients. The 24-page illustrated booklet gives details about the role of the mother in caring for the sick child and the importance of following the regimen prescribed by the physician. Instruction is included on bathing the child in bed, giving medicine, taking the pulse and temperature, and keeping records.

Red Cross Adopts Mouth-To-Mouth Lifesaving Method.—The American Red Cross officially adopted the mouth-to-mouth technique of artificial respiration for adults as well as children. Teaching of the method in Red Cross first aid and water safety courses will begin immediately. The technique was declared the most practical in a unanimous verdict of a committee of the National Academy of Sciences—National Research Council after a thorough review of artificial respiration data. The Red Cross delayed announcement of its adoption of the method only long enough to prepare and have published an instruction manual for use of its volunteer class instructors. Distribution of copies of this manual to the 3,700 Red Cross Chapters was completed early in July. The Red Cross still considers manual methods of artificial respiration acceptable for rescuers who cannot or will not use the mouth-to-mouth or mouth-to-nose technique. The two methods it recommends are the Nielsen back pressure-arm lift method and the Silvester chest pressure-arm lift method.

LATIN AMERICA

Research in Genetics by Brazilian Scientists.—Four Brazilian universities and the Brazilian Society of Genetics are cooperating in a major new program of research in human genetics with the help of five Rockefeller Foundation grants totaling $120,250. Brazilian geneticists have already made distinguished collaborative research on Drosophila population genetics. Their new cooperative program in human genetics will be planned primarily by the Brazilian Society of Genetics. The University of São Paulo is the first Brazilian school to offer a course in human genetics to medical students, and the first to develop a broad research program in the field. Research in human genetics already in progress at the University of Paraná, Curitiba, includes a study of consanguineous marriages in several Brazilian states. The University of Rio Grande do Sul, in Porto Alegre, will establish a human serum bank where antisera will be available to all investigators. Genetic studies on several Indian tribes, including one in an isolated region of the Amazon Basin, will be done by the University of Bahia in Salvador.

CORRECTION

Polyps of the Colon and Rectum.—In the article "Polyps of the Colon and Rectum" by Rider et al. (in THE JOURNAL, June 6, page 633) the term adenocarcinoma was used throughout in place of the term adenoma malignum, to agree with the terminology preferred in the fourth edition of Standard Nomenclature of Diseases and Operations. The authors have now stated that throughout their paper the meaning of adenocarcinoma is adenocarcinoma grade 1, or the synonyms adenocarcinoma in situ or adenoma malignum.

EXAMINATIONS AND LICENSURE

NATIONAL BOARD OF MEDICAL EXAMINERS

National Board of Medical Examiners: Various Centers: Part I only, Sept. 9-10. Examinations must be received at least six weeks in advance of a specific examination date. Examining centers established after close of registration. Exec. Sec., Dr. John P. Hubbard, 133 South 36th St., Philadelphia 4.

EDUCATIONAL COUNCIL FOR FOREIGN MEDICAL GRADUATES, INC.

Educational Council for Foreign Medical Graduates: Stations around the world, Sept. 22. Final date for filing applications was June 22. Succeeding examinations—March 16, 1960 and Sept. 21, 1960. Exec. Director, Dr. Dean F. Smiley, 1710 Orrington Ave., Evanston, Ill.

BOARDS OF MEDICAL EXAMINERS

ALABAMA: *Examination.* Montgomery, June 21-23, 1960. Sec., Dr. D. G. Gill, State Office Bldg., Montgomery.

ALASKA:* On application in Anchorage or Fairbanks. Sec., Dr. W. M. Whitehead, 172 South Franklin St., Juneau.

ARIZONA:* *Examination.* Phoenix, Oct. 14-16. *Reciprocity.* Phoenix, Oct. 17. Ex. Sec., Mr. Robert Carpenter, 826 Security Bldg., Phoenix.

ARKANSAS:* *Examination and Reciprocity.* Little Rock, Nov. 5-6. Sec., Dr. Joe Verser, Harrisburg.

CALIFORNIA: *Written.* Sacramento, October 19-22. *Oral.* Los Angeles, August 15; San Francisco, November 14. *Oral and Clinical.* Los Angeles, August 16; San Francisco, Nov. 15. Sec., Dr. Louis E. Jones, Room 536, 1020 N Street, Sacramento.

CONNECTICUT:* *Homepathic. Examination.* Derby, Sept. 8. Sec., Dr. Donald A. Davis, 38 Elizabeth St., Derby.

DISTRICT OF COLUMBIA:* *Examination.* Washington, Dec. 14-15. *Reciprocity.* Washington, Sept. 14. Deputy Director, Mr. Paul Foley, 1740 Massachusetts Ave., Washington 6.

FLORIDA:* *Examination.* Miami Beach, Nov. 22-24. Sec., Dr. Homer L. Pearson, 901 N.W. 17th St., Miami 36.

GEORGIA: *Examination and Reciprocity.* Atlanta, Oct. 13. Sec., Mr. Cecil L. Clifton, 224 State Capitol, Atlanta 3.

GUAM: *Subject to Call.* Act. Sec., Dr. F. L. Conklin, Agana.

INDIANA: *Examination.* Indianapolis, June 1960. *Reciprocity.* Indianapolis, fourth Wednesday of each month. Ex. Sec., Miss Ruth V. Kirk, 538 K. of P. Bldg., Indianapolis.

KANSAS:* *Examination and Reciprocity.* Kansas City, January 1960. Sec., Dr. F. J. Nash, New Brotherhood Bldg., Kansas City.

LOUISIANA: *Examination and Reciprocity.* New Orleans, Dec. 3-5. Sec., Dr. Edwin H. Lawson, 930 Hibernia Bank Bldg., New Orleans 12.

MARYLAND: *Examination.* Baltimore, Dec. 8-11, Sec., Dr. Frank K. Morris, 1211 Cathedral St., Baltimore 1.

MINNESOTA:* *Examination and Reciprocity.* St. Paul, Oct. 20-22. Sec., Dr. F. H. Magney, 230 Lowry Medical Arts Bldg., St. Paul 2.

MONTANA: *Examination and Reciprocity.* Helena, Oct. 6. Sec., Dr. Thomas L. Hawkins, 535 Fuller Ave., Helena.

NEBRASKA:* *Examination.* Omaha, June 13-15, 1960. Dir., Bureau of Examining Boards, Room 1009, State Capitol Bldg., Lincoln 9.

NEVADA:* *Examination and Reciprocity.* Reno, Sept. 8. Sec., Dr. G. H. Ross, 112 North Curry St., Carson City.

NEW HAMPSHIRE: *Examination and Reciprocity.* Concord, Sept. 9-12. Sec., Dr. Edward W. Colby, 107 State House, Concord.

NEW JERSEY: *Examination.* Trenton, Oct. 20-23, *Reciprocity.* Monthly, Sec., Dr. Royal A. Schaaf, 28 West State St., Trenton.

NEW MEXICO:* *Examination and Reciprocity.* Santa Fe, Nov. 16-17. Sec., Dr. C. Derbyshire, 227 East Palace Ave., Santa Fe.

NEW YORK: *Examination.* Albany, Buffalo, New York and Syracuse, Dec. 8-11. Sec., Dr. Stiles D. Ezell, 23 South Pearl St., Albany.

OHIO: *Examination.* Columbus, Dec. 15-17. *Endorsement.* Columbus, Aug. 26 and Oct. 5. Sec., Dr. H. M. Platter, 21 W. Broad St., Columbus 15.

OREGON:* *Examination.* Portland, Oct. 22-24. Ex. Sec., Mr. Howard I. Bobbitt, 609 Failing Bldg., Portland.

PUERTO RICO: *Examination.* San Juan, Sept. 8. Sec., Dr. Joaquin Mercado Cruz, Box 9158, Santurce.

SOUTH DAKOTA:* *Examination.* Sioux Falls, Aug. 25-26. Exec. Sec., Mr. John C. Foster, 300 First National Bank Bldg., Sioux Falls.

TENNESSEE:* *Examination.* Memphis, Sept. 23-24. Sec., Dr. H. W. Qualls, 1635 Exchange Bldg., Memphis 3.

TEXAS:* *Examination.* Fort Worth, Dec. 3-5. *Reciprocity.* Houston, Aug. 29-31. Sec., Dr. M. H. Crabb, 1714 Medical Arts Bldg., Fort Worth 2.

VIRGINIA: *Examination and Reciprocity.* Richmond, Dec. 2-4. Address: Board of Medical Examiners, 631 First St. S. W., Roanoke.

WYOMING: *Examination and Reciprocity.* Cheyenne, Oct. 5. Sec., Dr. James W. Sampson, State Office Bldg., Cheyenne.

BOARDS OF EXAMINERS IN THE BASIC SCIENCES

ALASKA: *Examination and Reciprocity.* Juneau, November. Sec., Dr. R. Harrison Leer, Alaska Office Bldg., Juneau.

ARIZONA: *Examination.* Tucson, Sept. 15. Sec., Mr. Herman E. Bateman, University of Arizona, Tucson.

COLORADO: *Examination.* Denver, Sept. 2-3. *Reciprocity.* Denver, Sept. 4. Sec., Dr. Esther B. Starks, 1459 Ogden St., Denver 18.

CONNECTICUT: *Examination.* New Haven, Oct. 10. Exec. Asst., Mrs. Regina G. Brown, 258 Bradley St., New Haven 10.

DISTRICT OF COLUMBIA: *Examination.* Washington, Nov. 23-24. *Reciprocity.* Washington, Sept. 14. Deputy Director, Mr. Paul Foley, 1740 Massachusetts Ave., Washington 6.

KANSAS: *Examination.* Pittsburg, Nov. 6-7. Sec., Dr. Leon C. Heckert, Kansas State College, Pittsburg.

MICHIGAN: *Examination.* Ann Arbor and Detroit, Oct. 9-10. Sec., Mrs. Anne Baker, West Michigan Ave., 116 Stevens T. Mason Bldg., Lansing.

MINNESOTA: *Examination.* Minneapolis, Oct. 6-7. Sec., Dr. Raymond N. Bieter, 105 Millard Hall, University of Minnesota, Minneapolis.

NEVADA: *Reciprocity,* Sept. 8. Sec., Dr. Kenneth C. Kemp, Box 9355, University of Nevada, Reno.

NEW MEXICO: *Reciprocity.* Santa Fe, Oct. 7. Sec., Mrs. M. Cantrell, P. O. Box 1522, Santa Fe.

OKLAHOMA: *Examination.* Oklahoma City, Sept. 25-26. Exec. Sec., Mrs. L. Haidek, 813 Braniff Bldg., Oklahoma City.

SOUTH DAKOTA: *Examination.* Vermillion, Dec. 4-5. Dr. Gregg M. Evans, 310 East 15th St., Yankton.

TEXAS: *Examination.* Austin, Oct. 12-13. Sec., Bro. Raphael Wilson, 407 Perry-Brooks Bldg., Austin.

WISCONSIN: *Examination.* Madison, Sept. 11 and Milwaukee, Dec. 5, Sec., Mr. Wm. H. Barber, 621 Ranson St., Milwaukee.

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*Basic Science Certificate required.

GOVERNMENT SERVICES

ARMY

Dr. Sim Honored.—Dr. Van M. Sim, chief of the Chemical Warfare Laboratories' clinical research division at Army Chemical Center, Maryland, was given the Army's highest civilian award, the Decoration for Exceptional Civilian Service. Dr. Sim was cited for "volunteering to be the first to expose himself to several new chemical agents at the risk of grave personal injury and the direction of a program whereby over 400 volunteers have been exposed without a single injury."

Personal.—Col. James T. McGibony, M. C., was appointed chief of the medical plans and operations division in the office of the surgeon general thereby succeeding Col. Angel A. Cardona, M. C., who is now surgeon of the military district of Washington.

NAVY

Personal.—Capt. Clifford P. Phoebus, M.C., U. S. Navy, recently reported to the Bureau of Medicine and Surgery for duty as director, Astronautical Division.

VETERANS ADMINISTRATION

Personal.—Dr. Frederick J. Rachiele, formerly director of professional services at the Veterans Administration hospital in Denver, Colo., wa appointed manager of the Tucson, Ariz., VA hospital.

PUBLIC HEALTH SERVICE

Directory of Research Fellows.—The National Cancer Institute has published the first directory of its research fellows since the fellowship program was established in 1937. Section 1 of the directory contains the names of 924 persons whose fellowships were completed prior to April 1, 1958, and section 2 contains the names of 245 persons whose fellowships extended beyond that date. A brief statement about each fellow tells the highest degree he held at the time of his appointment, the name of the school granting the degree, the type, duration, and place of his fellowship, and the name of the research project. The present position of those whose fellowships had terminated by April 1, 1958, is also given. The introduction to the directory discusses the history of the program, which was the first of its kind to be supported by the federal government.

Most of the former fellows are now engaged in research or teaching or both. About half of the fellows appointed in the early years of the institute are now permanent members of the institute's staff in key research positions, and a number of the later fellows have also joined the staff. Copies of the directory (Research Fellows of the National Cancer Institute, 1938-1958) were sent to the libraries of appropriate institutions, including four-year colleges, medical schools, and foundations supporting research. Copies are also on sale by the Superintendent of Documents, Government Printing Office, Washington 25, D. C., for 45 cents a copy.

Appointments to Selection Committee for Senior Research Fellowships.—Drs. Kimball C. Atwood, of the department of obstetrics and gynecology at the University of Chicago; Howard C. Hopps, chairman of the pathology department at the University of Texas; Eli D. Goldsmith, professor of histology and research coordinator at New York University College of Dentistry; Antonio Ciocco, head of the department of biostatistics at the University of Pittsburgh's Graduate School of Public Health; and John B. Graham, professor of pathology at the University of North Carolina, were appointed to serve three-year terms on the selection committee for the Senior Research Fellowship program of the National Institutes of Health. They will advise and make recommendations to the surgeon general on the selection of qualified persons for the five-year fellowships. The fellowship awards are designed principally for promising young scientists sponsored by preclinical departments in the period between the completion of their postdoctoral research training and their eligibility for permanent higher academic appointments. Under special circumstances, senior scientists may be awarded these fellowships to supply needed strength in preclinical science departments.

Personal.—Dr. Henry S. Kaplan, professor of radiology at Stanford University School of Medicine, and Dr. Stanhope Bayne-Jones, well-known medical educator, were appointed to four-year terms as members of the National Advisory Cancer Council, effective Oct. 1. In this capacity they will advise and make recommendations to the surgeon general regarding research activities of the National Cancer Institute. The council is composed of 12 members, 6 of whom are leaders in science and 6 leaders in education and public affairs.

FEDERAL AVIATION AGENCY

Civil Air Surgeon Appointed.—Dr. James L. Goddard was appointed civil air surgeon of the Federal Aviation Agency. He is the first to hold this title, although the post had been filled on an acting basis by Dr. John E. Smith. Dr. Smith is now chief of the research requirements in the office of the civil air surgeon. The civil air surgeon is concerned with the mental and physical fitness of airmen and air traffic controllers and the chief of the research requirements division is responsible for the application of findings of aeromedical research to civil aviation.

DEATHS

Bauer, Wesley Warren ⊛ Fort Morgan, Colo.; (licensed in Colorado in 1920); died May 31, aged 64.

Benson, Theodore J. ⊛ Fromborg, Mont.; University of Minnesota College of Medicine and Surgery, Minneapolis, 1904; served as mayor and member of the school board; died in the Deaconess Hospital, Billings, June 2, aged 85.

Bronson, Malcolm ⊛ Hamilton, Ohio; Miami Medical College, Cincinnati, 1908; died May 31, aged 74.

Buckingham, Edwin Wheeler II ⊛ Newport News, Va.; Medical College of Virginia, Richmond, 1918; veteran of World War I; served as a medical missionary in China; associated with the Riverside Hospital, where he was secretary-treasurer of the medical staff from 1931 to 1947; recently honored as the city's Doctor of the Year; died June 6, aged 66.

Canright, Harry Lee, St. Cloud, Fla.; University of Michigan Department of Medicine and Surgery, Ann Arbor, 1889; for many years a medical missionary in China; died May 28, aged 94.

Clauser, Eldo Horace Mann ⊛ Muncie, Ind.; born in Owasco, Ind., March 27, 1890; Indiana University School of Medicine, Indianapolis, 1915; past-president and charter member of the Muncie Academy of Medicine; past-president of the Delaware–Blackford Counties Medical Society; fellow of the American College of Surgeons, of which he was a member of the board of governors from 1955 to 1958, and a past-president of the Indiana Chapter; served as chairman of the executive committee and member of the council of the Indiana State Medical Association; founding member of the U. S. Committee of the World Medical Association; since its inception, chairman of the Indiana Hospital Licensing Committee; veteran of World War I; a member of the board of governors of the Blue Shield; a member of the board of directors of the local YMCA; past-president of the Muncie Kiwanis Club and the local Indiana University Alumni Association; for many years chairman of the executive committee of the staff of Ball Hospital, where he died May 31, aged 69.

Cooney, M. Blanche ⊛ West Newbury, Mass.; Tufts College Medical School, Boston, 1911; served on the staff of the Hale Hospital in Haverhill; died May 23, aged 69.

Culbertson, Ora J. ⊛ Belleville, Ill.; St. Louis University School of Medicine, 1902; fellow of the American College of Surgeons; associated with the St. Mary's and Christian Welfare hospitals; died May 29, aged 81.

Driskell, Cecil Rogers ⊛ Springfield, Ill.; St. Louis University School of Medicine, 1906; past-president of the Montgomery County Tuberculosis Association; died in St. John's Hospital May 20, aged 74.

Gallagher, James S. ⊛ St. Petersburg, Fla.; Temple University School of Medicine, Philadelphia, 1909; for many years practiced in Philadelphia; died in the Episcopal Hospital, Philadelphia, June 4, aged 74.

Gallaspy, Glenn Todd ⊛ West Monroe, La.; Emory University School of Medicine, Atlanta, 1931; associated with St. Francis Hospital in Monroe, where he died May 30, aged 51.

Gerstner, David, Kansas City, Mo.; Eclectic Medical University, Kansas City, 1918; died May 28, aged 80.

Ghormley, Ralph Kalb ⊛ Carmel, Calif.; born in Portland, Ore., Feb. 10, 1893; Johns Hopkins University School of Medicine, Baltimore, 1918; following service as a medical officer with the American Expeditionary Forces, interned at Johns Hopkins Hospital and Children's Hospital in Baltimore and the New York Hospital in New York City; in 1921-1922 assistant resident surgeon at Johns Hopkins Hospital in Baltimore; entered the practice of orthopedic surgery in Boston, where in 1922-1923 he was an assistant in orthopedic surgery at Harvard Medical School, and later an instructor; served as attending orthopedic surgeon to the Massachusetts General Hospital in Boston; came to Rochester, Minn., in September, 1929, as a consultant in orthopedic surgery at the Mayo Clinic and assistant professor in Mayo Foundation, Graduate School, University of Minnesota; advanced to associate professor in 1932 and full professor in 1937 and, in 1938, became head of the orthopedic section of the Mayo Clinic, a post he held until 1955, when he became a senior consultant; specialist certified by the American Board of Orthopedic Surgery, of which he was past-president; past-president and secretary of the American Orthopedic Association; past-president of the Clinical Orthopaedic Society; elected president of the staff of the Mayo Clinic in 1952 and served as president of the Mayo Foundation Chapter of the Society of the Sigma Xi in 1943-1944; member of the Western Surgical Association, American Academy of Orthopedic Surgeons, American Association for the Sur-

⊛ Indicates Member of the American Medical Association.

gery of Trauma, the Robert Jones Orthopedic Society, International Society of Orthopedic Surgery and Traumatology, the Alpha Omega medical honor society, the Harvard Club of Boston, and the Alumni Association of the Mayo Foundation; a corresponding member of the Scandinavian Orthopedic Society; fellow of the American College of Surgeons; in 1954 received a certificate of merit from the American Medical Association for an exhibit on Primary Tumors of the Soft Tissues of the Extremities Exclusive of Epithelial Tumors—An Analysis of 500 Consecutive Cases and in 1956 received a certificate of merit for exhibit on Bone Tumors; served on the staffs of the St. Mary's and Colonial hospitals in Rochester, Minn.; a consultant in his specialty to the U. S. Veterans Administration; served as a member of the advisory committee of the Children's Bureau of the U. S. Department of Labor; in 1942 gave the William J. Mayo Clinic Lecture at the University of Michigan in Ann Arbor; in 1957 was honored by former fellows in orthopedic surgery of the Mayo Foundation and colleagues at the Mayo Clinic with the establishment of the Ralph K. Ghormley Traveling Scholarship; joint author of "Diagnosis in Joint Disease: a Clinical and Pathologic Study of Arthritis"; editor of a volume "Orthopedic Surgery" published in 1938; associated with Monterey (Calif.) Hospital and the Peninsula Community Hospital, where he died June 6, aged 66.

Glasener, Charles F., Bradenton, Fla.; Loyola University School of Medicine, Chicago, 1916; for many years on the staff of the Elmhurst (Ill.) Community Hospital; died in the Manatee Veterans Memorial Hospital May 28, aged 76.

Glickman, Abraham Jacob ⊗ Boston; University of St. Vladimira Faculty of Medicine, Kiev, Russia, 1904; died April 27, aged 80.

Greer, Charles Edward ⊗ Charleston, Ill.; Chicago Homeopathic Medical College, 1898; veteran of World War I; member of the honorary staff of the Charleston Community Memorial Hospital, where he died June 1, aged 84.

Griffin, Silas ⊗ St. Petersburg, Fla.; Kentucky University Medical Department, Louisville, 1900; for many years practiced in Henderson, Ky.; served as secretary of the Henderson County (Ky.) Medical Society and health officer of Henderson County; died in St. Anthony Hospital May 25, aged 83.

Hahn, Charles David, Baltimore; Medical College of Ohio, Cincinnati, 1897; died June 4, aged 86.

Hanley, James Leo ⊗ Bridgeport, Conn.; Yale University School of Medicine, New Haven, 1935; certified by the National Board of Medical Examiners; interned at University Hospitals in Cleveland; served a residency at the Woman's Hospital in Detroit; formerly a fellow at the Mayo Foundation in Rochester, Minn.; veteran of World War II; associated with Bridgeport Hospital and St. Vincent's Hospital, where he died May 31, aged 49.

Harris, Abraham J. ⊗ Newton, Mass.; Mid-West Medical College, Kansas City, Mo., 1934; died May 30, aged 66.

Hathaway, Alfred H. ⊗ Mountain View, Okla.; University of Arkansas School of Medicine, Little Rock, 1905; died May 25, aged 87.

Heitmann, Kenneth Arnold Conrad ⊗ Santa Ana, Calif.; University of Michigan Medical School, Ann Arbor, 1935; specialist certified by the American Board of Radiology, Inc.; member of the American College of Radiology; died May 26, aged 49.

Hickman, John Samuel ⊗ Meridian, Miss.; Mississippi Medical College, Meridian, 1911; served as a member of the state legislature; for many years superintendent of the East Mississippi Hospital; died in the Rush Memorial Hospital May 31, aged 75.

Holt, Robert Edward Lee, Portland, Ore.; University of Oregon Medical School, Portland, 1908; served on the staff of the Providence Hospital, where he died June 1, aged 78.

Kass, Paul, Miami Beach, Fla.; University of Virginia Department of Medicine, Charlottesville, 1928; died in North Miami May 26, aged 56.

Kitchens, Orren William ⊗ Byromville, Ga.; Atlanta Medical College, 1915; vice-chairman of the Dooly County Board of Commissioners; member of the city council for 42 years; on the staff of the Riverside Hospital in Montezuma; a director of the Byromville Bank; died in the Montezuma (Ga.) Hospital June 1, aged 67.

Koll, Irvin Sunthimer, Beverly Hills, Calif.; Rush Medical College, Chicago, 1907; specialist certified by the American Board of Urology; member of the American Urological Association; formerly practiced in Chicago, where he was associated with the Michael Reese Hospital, where in 1956 he was awarded a bronze plaque for at least 30 years service; author of "How to Stay Healthy"; died May 30, aged 75.

Kuykendall, Pere Moran ⊗ Ranger, Texas; Baylor University College of Medicine, Dallas, 1917; past-president of the Eastland County Medical Society; veteran of World War I; served as medical director of the West Texas Hospital; past-president of the Chamber of Commerce, Eastland County Water Board, and Rotary Club; served as a member and president of the Eastland County School Board; died in the Ranger General Hospital May 28, aged 66.

Lang, Charles Albert, New York City; University of Toronto Faculty of Medicine, Toronto, Ont., Canada, 1898; retired assistant attending in pediatrics at the Presbyterian Hospital, where he died June 1, aged 83.

Leach, Charles Henry ⊗ Tenants Harbor, Maine; Medical School of Maine, Portland, 1899; died in Rockland May 25, aged 85.

Levy, Simon Cuthbert, Plaquemine, La.; Medical Department of Tulane University of Louisiana, New Orleans, 1897; associated with the Plaquemine Sanitarium, where he died June 1, aged 86.

Linsin, Ivan M., St. Petersburg, Fla.; Bennett Medical College, Chicago, 1910; formerly associated with the Indian Service; died in Tampa May 29, aged 72.

Luce, Rey Vincent ⊗ Santa Rosa, Calif.; Rush Medical College, Chicago, 1913; fellow of the American College of Surgeons; veteran of World War I; formerly practiced in Akron, Ohio, where he was chief of staff at Akron City Hospital; past-president of the Summit County (Ohio) Medical Society; died in Boyes Springs, May 30, aged 71.

Marchman, Oscar Milton ⊗ Dallas, Texas; born in Jefferson, Texas, April 5, 1872; Missouri Medical College, St. Louis, 1899; also a pharmacist; specialist certified by the American Board of Otolaryngology; member of the American Academy of Ophthalmology and Otolaryngology; fellow of the American College of Surgeons; served as secretary of the Texas Ophthalmological and Otolaryngological Society; first president of the Dallas Academy of Medicine, which he helped organize; past-president of the Dallas Southern Clinical Society and the Dallas Academy of Ophthalmology and Otolaryngology; oldest active member of the Dallas County Medical Society, of which he was past-president, was recently given the "Golden Deeds" award by the Dallas Exchange Club for his "unselfish service"; emeritus professor of otolaryngology, Southwestern Medical School of the University of Texas; formerly on the faculty of the Baylor University College of Medicine; at one time secretary of the city board of health; past-president of the Dallas chapter of the American Red Cross; helped organize the Dallas Health and Science Museum, of which he was a trustee; associated with the Baylor University Hospital, Medical Arts Hospital, and Children's Medical Center; died in the Baylor University Hospital May 25, aged 87.

Mathers, James Andrew, Kingston, N. Y.; University of Toronto Faculty of Medicine, Toronto, Ont., Canada, 1917; veteran of World War I; member of the staffs of the Kingston and Benedictine hospitals; died May 19, aged 65.

Matthews, Charles B. ⊗ Hammond, Ind.; Kentucky School of Medicine, Louisville, 1894; veteran of World War I; associated with St. Margaret Hospital; died May 30, aged 86.

Nicholls, James Benton ⊗ Windsor, N. C.; University of Maryland School of Medicine, Baltimore, 1910; member of the American Trudeau Society; in February, 1953, a new building at the Catawba Sanatorium was named in his honor and later that year he retired as superintendent and medical director, after many years of service; died May 15, aged 71.

Noe, Carl Abraham ⊗ Cedar Rapids, Iowa; State University of Iowa College of Medicine, Iowa City, 1929; specialist certified by the American Board of Ophthalmology and the American Board of Otolaryngology; member of the American Academy of Ophthalmology and Otolaryngology and the Association for Research in Ophthalmology; served as secretary treasurer of the Iowa Academy of Ophthalmology and Otolaryngology; veteran of World War II; associated with Methodist Hospital, St. Luke's Hospital, where he was president-elect of the staff, and the Mercy Hospital, where he died May 26, aged 54.

Philp-Bradshaw, Martha, San Francisco; Dalhousie University Faculty of Medicine, Halifax, N. S., Canada, 1902; for many years a medical missionary in China; died May 29, aged 89.

Powell, Eppie Clifton, Middlesex, N. C.; University of Nashville (Tenn.) Medical Department, 1907; chairman of the Nash County Board of Health and Middlesex School Board; for many years physician to the Free Will Baptist Orphanage; a director of Peoples Bank & Trust Company; past-president of the Middlesex Rotary Club; died in the Wayne Memorial Hospital, Goldsboro, May 26, aged 75.

Ray, Fred Merton ⊗ Pocatello, Idaho; Northwestern University Medical School, Chicago, 1909; veteran of World War I; associated with St. Anthony Hospital and Bannock Memorial Hospital, where he died May 29, aged 77.

Roark, Jesse Lawrence, Albuquerque, N. M.; born in Water Valley, Miss., Sept. 30, 1895; Jefferson Medical College of Philadelphia, 1924; served overseas during World War I; interned at the Jefferson Medical College Hospital in Philadelphia and served a residency at the White Haven Sanitorium in White Haven, Pa.; at one time on the teaching staff of his alma mater; formerly medical director of Lafayette and Yalobusha counties in Mississippi; served on the staffs of the Mississippi State Sanatorium for Tuberculosis in Sanatorium, Pennsylvania State Sanatorium for Tuberculosis in South Mountain, Pa., Essex County Sanatorium for Tubercular Diseases in Verona, N. J., and the Arkansas

Tuberculosis Sanatorium in State Sanatorium; died in the Veterans Administration Hospital May 31, aged 63.

Roth, Charles Rudolph ® Chicago; Northwestern University Medical School, Chicago, 1906; associated with the Illinois Masonic Hospital; died June 8, aged 82.

Russell, Grover Cleveland ® Jackson, Miss; Medical Department of Tulane University of Louisiana, New Orleans, 1909; at one time practiced in Johns, serving as health officer of Rankin County for many years; associated with the Mississippi Baptist Hospital; died June 8, aged 74.

Russell, Marion Fore ® Great Bend, Kan.; born in Alma, Va., Aug. 23, 1884; University of Pennsylvania Department of Medicine, Philadelphia, 1907; past-president of the Barton County Medical Society; fellow of the American College of Surgeons and president of the Kansas Chapter; served as county coroner; for many years associated with the Boy Scout movement and in 1943 was honored with the Silver Beaver Boy Scout award; member of the staff of St. Rose Hospital, where he was chief of staff from 1937 to 1945; past-president of the Great Bend Rotary Club; a director of the American State Bank; vice-president and a director of the Prudential Building & Loan Association; died May 31, aged 74.

Sanford, Benjamin Bentley ® Portland, Maine; Tufts College Medical School, Boston, 1924; veteran of World War II; served as a colonel in the U. S. Air Force Reserve; died May 25, aged 59.

Stadulis, Ignatius Martin, Wilkes-Barre, Pa.; Jefferson Medical College of Philadelphia, 1924; veteran of World War I; medical inspector for Hanover Township schools for many years; on the staff of the Mercy Hospital; died June 1, aged 60.

Stanley, Thomas Eldridge ® Richmond, Va.; Medical College of Virginia, Richmond, 1932; interned at the Hospital of St. Vincent de Paul; served as chairman of the school board of Hanover County; a staff member of St. Elizabeth's Hospital, where he died June 3, aged 50.

Stewart, James Leon, New York City; Université de Lyon Faculté de Médecine et de Pharmacie, France, 1919; associated with the French Hospital, where he died April 19, aged 67.

Schnitzler, Friedrich Wilhelm ® Woodmere, N. Y.; Albert-Ludwigs-Universität Medizinische Fakultät, Freiburg, Baden, Germany, 1921; died May 22, aged 69.

Stone, William Ernest ® Boonville, Mo.; Washington University School of Medicine, St. Louis, 1918; veteran of World Wars I and II; past-president of the Cooper County Medical Society; past-chief of staff at St. Joseph Hospital; died in the Veterans Administration Hospital, Wadsworth, Kan., May 14, aged 67.

Tinsman, Eugene, Orient, Iowa; Keokuk (Iowa) Medical College, College of Physicians and Surgeons, 1903; served on the school board for many years; member of the medical examining board for the World War II draft and received a citation signed by President Franklin D. Roosevelt and a selective service medal from Congress; died May 24, aged 85.

Watson, Cassius Hinds ® Brookfield Center, Conn.; Long Island College Hospital, Brooklyn, 1905; served on the faculty of his alma mater; medical director of the American Telephone and Telegraph Company from 1915 to Oct. 1, 1943, when he retired; past-president of the National Safety Council and the American Association of Industrial Physicians and Surgeons; fellow of the American College of Surgeons; formerly associated with the Bushwick and Eastern District hospitals in Brooklyn; past-president of the Stony Wold Sanatorium in Lake Kushaqua, N. Y.; died in Stamford, June 1, aged 80.

Webster, Hugh Martin Jr., Huntsville, Ala.; Vanderbilt University School of Medicine, Nashville, Tenn., 1950; veteran of World War II; died May 30, aged 32.

Wellman, Graham Ormond, Carthage, Mo.; Hahnemann Medical College and Hospital of Philadelphia, 1913; served in France during World War I; died May 28, aged 76.

Williams, Tom Alfred, London, England; University of Edinburgh Faculty of Medicine, Edinburgh, Scotland, 1896; for many years practiced in Washington, D. C.; past-president of the Washington Psychological Society and the Washington Society of Nervous and Mental Diseases; died in Bournemouth, England, May 27, aged 89.

Yale, Arthur Wells, San Diego, Calif.; Hahnemann Medical College and Hospital of Philadelphia, 1899; veteran of World War I; died in Bellflower May 23, aged 83.

Zeller, Raymond Bryant ® Hazlehurst, Miss.; Jefferson Medical College of Philadelphia, 1927; member of the American Academy of General Practice, American Association for the Advancement of Science, and the American Association of Railway Surgeons; for many years secretary of the Tri-County Medical Society; veteran of World War I; past-vice-president of the Jefferson Medical College Alumni Association; past-president of the staff, Hardy Wilson Memorial Hospital; died June 4, aged 58.

FOREIGN LETTERS

BRAZIL

Intestinal Schistosomiasis.—Many surveys carried out in different areas have demonstrated that schistosomiasis, imported from Africa with Negro slaves and neglected for decades, now affects about 4 million persons in Brazil, mainly in the northern tropical section. Federal and state control programs are now yielding appreciable results. At a meeting of the Rio de Janeiro Medical and Surgical Society Dr. Mario Pinotti, Minister of Health, said that in infected districts of seven states the disease is being combated intensively with several methods of attack; in 8 others, where the problem is less severe, only partial measures are being used; and in the remaining states and territories schistosomiasis has not been reported.

The control measures include the use of such chemical molluscacides as copper sulfate and sodium pentachlorophenate. Three or four times a year snail-infested waters are treated with 1 Gm. of the latter per 100 liters. Sanitary engineers are also building water purification systems in rural communities and constructing bath houses and communal laundries with clean water supplies. Unsanitary lakes and streams are being placarded with warning posters. Another measure adopted to combat the disease is the mass treatment of infected persons, with tartar emetic, emetine, stibophen, lucanthone, and other drugs. Free treatment centers were installed by the Ministry of Health. Twenty-seven communities were freed from the disease in 1958, but they must be protected by a strict control of internal migrations of the population.

Gallstone Ileus.—J. von Sonnleithner, of Sanatório São Lucas in São Paulo, operated on a patient with gallstone ileus in whom a large migrating calculus stopped in the first part of the jejunum. This was the 26th such case reported in Brazil. Last year, Helio Silva (*Bulletin of the Brazilian College of Surgeons*) collected a series of 500 such cases from the world literature. In this series the sex ratio was one man to seven women. Most of the patients were over 50 years of age.

Complications After Pulmonary Resection.—Although adequate preoperative treatment and more precise indications in pulmonary resections have markedly lowered the incidence of postoperative complications, such complications after resections for treatment of tuberculosis are still rather frequent. C. Frazzato Jr. and co-workers of the São Paulo Hospital (*Rev. paulista med.* 54:253, 1959) treated 31 patients with pulmonary tuberculosis who had had adequate medical treatment for at least one year. During the preoperative preparation of the patients treatment with isoniazid and streptomycin was continued. In two of four patients given penicillin and streptomycin by inhalation a remission occurred. The remaining patients were operated on. Para-aminosalicylic acid was not used in the preoperative preparation, although some patients had received this drug in previous ambulatory treatment.

The basic indication for resection was a residual lesion after adequate treatment, with or without positive sputum. All patients had obligatory indications for operation: 13 had a cavity in an upper lobe; 6 a cavity in the middle or a lower lobe; 6 fibrosis, atelectasis, and bronchiectasis; one an extensive unilateral lesion and residual lesion after thoracoplasty; and one a tuberculoma of the base of the right lung. Thirty-two resections (10 pneumectomies, 17 lobectomies, and 5 lobectomies with segmentary resections) were performed in the 31 patients. The cavities of all patients were drained under water, since this is a routine procedure at that hospital, where drainage is considered useful postoperatively. Other postoperative measures included antibiotic treatment, sedation (without morphine), early ambulation, fluids by mouth, and specific antituberculosis treatment.

The authors observed 54 complications (not counting 2 of a general surgical nature): residual sack in 10, suppuration in 9, fistula in 8, empyema in 8, shock in 4, hemothorax and pleural hemorrhage in 3, atelectasis and secretions in 2, reactivation in 2, cardiac insufficiency in 2, subcutaneous emphysema in 2, respiratory insufficiency in 2, and total dehiscence in 2. Such complications occurred in 22 patients, but in 6 the complications were so mild (e. g., small effusion or scanty suppuration) that these patients can be grouped with the remaining 9, thus making a total of 15 patients with results considered excellent. Six patients were cured after complications, two continued to have sputum positive for tubercle bacilli, and eight died. The length of postoperative hospitalization was markedly increased by the complications. Fistulas were the most serious complications. Pneumectomy revealed itself as a major surgical risk, since 6 of the 10 patients on whom it was performed died. Serious complications always followed this type of operation and were usually fatal.

The items in these letters are contributed by regular correspondents in the various foreign countries.

The anesthetist has an important role in meeting the problems of secretion. The endobronchial intubations and the tamponment of the drainage bronchus must be the rule in pulmonary resections. Besides preventing internal drowning they permit a better surgical technique. Adequate chemotherapeutic and antibiotic treatments of tuberculosis in the preoperative and postoperative periods not only diminish the incidence of complications but also permit more boldness in the operative indications. Thus, patients with severe infections, cavitation, and even empyema with bronchial fistula can be operated on with success.

Blastomycosis.—J. Machado Jr. and J. L. Miranda (*O Hospital*, May, 1959), reported an epidemiologic study of South American blastomycosis. Between November, 1949, and January, 1959, they studied a series of 238 patients. Those most severely affected were in the 40-to-49-year-old group. There was no indication of frequency related to race. Women were less affected than men, but this was probably due to occupational factors. The infection was most common in farmers. The portals of entry of the parasite were the skin and the mucosa of the respiratory and digestive tracts, especially the oral muscosa.

Paranasal Tumors.—J. F. Barbosa, chief surgeon of the head and neck department of Central Institute of Cancer in São Paulo, analyzed a series of 141 patients with malignant tumors of the paranasal cavities. Of these 116 were Caucasian, 21 Negro, and 4 Oriental; 97 were men and 44 were women. Most of the patients were between the ages of 40 and 70 years. The author treated such patients by removing the upper portion of the ascending branch of the mandible, the lower portion of the temporal muscle, the upper portion of the masseter, the zygomatic arch, and all of the external pterygoid muscle. He exposed, tied, and severed the internal maxillary artery before removing the tumor. All the contents of the orbital cavity and the ethmoid sinus were included in the resected mass. As a rule, he covered the operative cavity with a free flap. The results of this treatment were encouraging.

Pancreatic Cysts.—Although pancreatic cysts are rare, four cases were presented by J. R. Alves, professor at the University of Minas Gerais, in Belo Horizonte. Two were true cysts and two were pseudocysts. In all the patients the diagnosis of pancreatic cyst was made preoperatively. In one there was a concomitant disease of the extrahepatic bile passages. In one there was a simultaneous occurrence of diabetes and trypanosomiasis. One case was probably due to a chronic pancreatitis with pancreatic fibrosis. There is no standardized operation for all cases. Splenectomy was necessary in two cases, owing to the extensive adhesions between the cyst and the spleen. All the patients recovered and returned to their normal activities.

DENMARK

Peptic Ulcers due to Corticosteroids.—A series of 10 patients who had peptic ulcers that developed during long-term steroid therapy with relatively small doses was reported by Aagaard and co-workers (*Acta chir. scandinav.* 116:423-428, 1958-1959). The ulcer involved the stomach in seven, the pylorus in two, and the jejunum in one. All 10 patients were operated on and had no postoperative complications. These ulcers were similar to ordinary gastric ulcers, apart from a less dramatic course during perforation. The steroids have two effects that might be assumed to be important in the development of peptic ulcers; they increase the production of hydrochloric acid and pepsin, and they inhibit fibroblast proliferation during wound healing and delay the formation of granulation tissue.

Types of Honors.—When one has reached the age of 70, or thereabouts, and has had a distinguished career, one's admirers may wish to express their appreciation by a collection containing original articles—many perhaps of great value. When such a volume is published by itself and not as a part of, or supplement to, a well-established medical journal, it often escapes the notice of librarians and others engaged in indexing and cataloging medical literature. The smallness of the mailing lists of some collections of this sort may contribute to the burial of their contents. To escape this fate B. Ibsen (*Nordisk medicin*, April 23, 1959) presented some alternatives. If the collection is to survive as such, it must be published in a medical journal with a substantial mailing list. If such a literary testimonial is not contemplated, the prospective contributors might find a channel for their emotions in the establishment of a prize to be given in the name of their idol. The award, from time to time, of this prize to some worthy recipient would remind the world of its debt. On the other hand, a fund collected in honor of the distinguished scientist might be earmarked for the remuneration of lecturers on given subjects. The author's pet idea, however, was to send the beloved septuagenarian on a journey to enlighten others by giving lectures himself.

Rehabilitation of the Nervous Patient.—K. H. Backer has published, through the University of Copenhagen, a monograph in which he reviews, from the point of view of rehabilitation, the fate of the patients discharged from the surgical and medical wards of a large Danish hospital in 1949. The rehabilitation movement at first stressed such dramatic ailments as paralysis, spasticity, blindness,

deafness, and crippling. These tended to overshadow the less striking mental handicaps, which, in the form of mild neurosis, psychopathy, or just slight mental deficiency, have interfered with wage-earning and a congenial mode of life. The author makes an urgent plea on behalf of the latter group.

Two 50-Year Jubilees.—In 1909 the National Health Service (NHS) and the Medical Jurisprudence Council came into being. Both have earned the general esteem they now enjoy by the skill with which their leaders have made them indispensable to the community. The present head of the former body, J. Frandsen (*Ugeskrift for laeger*, April 23, 1959), states that his predecessors had to fight in order to fit adequately into the machinery of a modern welfare state. With responsibilities to such important activities as dentistry, nursing, and pharmacy, to mention only three of the many spheres in which the NHS is interested, it acts in rather an advisory than a disciplinary capacity, not being a ministry of health nor the health department of some ministry or other. It is an autonomous institution, beyond the bounds of a central administration although connected with it and with local administrations. So long as the health activities of the country are decentralized, the NHS can successfully meet the calls made on it.

In *Ugeskrift for laeger* for April 30, Prof. K. Sand, head of the Medical Jurisprudence Council for over 30 years, traced its history since its birth in 1909. Here, too, is a record of prodigious growth from modest beginnings. With the growth of a third powerful organization, the Danish Medical Association, which works in close cooperation with the NHS, Denmark has built up a system of public health which may well serve as a model for other countries.

Pertussis Vaccination.—At the state serum institute in Copenhagen tests have been made for some time with a triple vaccine against diphtheria, tetanus, and pertussis, with a view to observing the severity and frequency of its side-effects. While awaiting a final verdict attention is being focused on pertussis vaccine alone, as given to prevent whooping cough early in infancy. As pointed out by H. Lautrop and co-workers (*Ugeskrift for laeger*, May 21, 1959) whooping cough continues to take a heavy toll of life in Denmark, with an average of about 25 deaths a year. About 75% of these occur in children under 1 year of age. There is also an unknown number of cases of bronchiectasis and other sequels to whooping cough that are not immediately fatal, hence the advice to start vaccination against it as early as the 5th week of life. Two further injections should then be given at intervals of a month, to be followed about a year later by a fourth injection. In the absence of such prophylactic vaccination it may be permissible to fall back on therapeutic injections just before or at the outbreak of whooping cough, but no extravagant claims can be made for such action.

Addiction to Tranquillizers.—J. Schou (*Ugeskrift for laeger*, April 23, 1959) stated that in 1958 over 24 million grams (61 million 400-mg. tablets) of meprobamate was sold. It is so popular with would-be suicides that 33 cases have already been reported in which it was the sole agent, in amounts varying from 8 to 40 Gm., in an attempt to commit suicide. None of these attempts proved fatal. In another series of attempted suicides in which meprobamate was given with a barbiturate there were two deaths. Although there were no deaths in the first series, the author warned against a too light-hearted prognosis, as only 6 Gm. given by mouth may induce a dangerous comatose intoxication. The risk of meprobamate addiction is now regarded as being so serious in Denmark that the author warned against its use for the cure of tobacco addiction.

Thallium Poisoning.—A discussion at a recent meeting of the Danish Society for Internal Medicine (*Nordisk medicin*, May 21, 1959) showed how polymorphous the manifestations of poisoning with thallium may be, whether it is taken in an attempt to commit suicide or by accident. In one series of six cases there were five in which thallium destined for rats and mice had been taken by mistake. Alopecia has been said to be a sure sequel to thallium poisoning, but it was observed in only two of these cases. The diagnosis of thallium poisoning may be comparatively easy when the characteristic alopecia appears several days after the poison has been taken, but it is less so when the clinical findings are suggestive of poliomyelitis. One of the patients in the above-mentioned series underwent a laparotomy, since violent colic had seemed to indicate thrombosis of some mesenteric vessel. One speaker at this meeting stressed the diagnostic value of tests of the urine for thallium, which in one of his patients was found in such quantities as to indicate that a lethal dose had been taken. As a result of prompt action the patient recovered, however.

FINLAND

Postoperative Biliary Stones.—Operations for biliary stones are sometimes complicated by concrements retained in the biliary ducts. A conservative method for the removal of such concrements is based on the lipid-dissolving property of ethyl ether. The chief reasons for the retention of stones in the biliary ducts are that they are situated high in the hepatic ducts, whence they may later migrate with the bile flow down into the common bile duct; or that by

the action of inflammatory processes the stones may become imbedded in the wall of the common bile duct or hidden in a cystlike cavity near the duodenal papilla, thus escaping observation; or, finally, that obesity or impaired general condition may limit the surgical possibilities and render operative cholangiography difficult. Alfthan and Köhler (*Acta chir. scandinav.* 116:437-449, 1958-1959) reported on 24 patients aged 27 to 68 years, in whom postoperative residual biliary tree stones were found. These patients represented 1.4% of all who had had operations for gallstones performed in the period 1954-1958. Of the 24 patients 14 were relieved of stones. From a clinical point of view ethyl ether seemed to be the best of all lipid solvents. Chemical analysis or, at any rate, a dissolving test in vitro before treatment, was recommended.

In the beginning the treatment should be cautious. Either the initial doses of ether should be small (about 0.5 ml.) or the ether should be given through a double-barreled tube, allowing the vapor to escape when the pressure rises. The authors did not observe any harmful side-effects of the ether. Concrements larger than 1 cm. in diameter can seldom be dissolved, and therefore comparatively early reoperation for such stones is indicated. Intrahepatic stones dissolve slowly and demand persistence. Small, common-duct stones generally dissolve within two to three weeks. A single dose of ether remains in the biliary ducts for about 10 minutes. The authors therefore recommended frequent treatments, prolonging the action of the ether as much as possible each time. Operative cholangiographies of a high technical standard probably afford the best possibility of visualizing stones in the biliary tree and should be made, if possible. If, however, stones persist in the biliary ducts, the authors recommend ether treatment first. Only if this procedure failed should reoperation be performed.

INDIA

Induced Cardiac Arrest.—A. K. Basu and co-workers (*Indian Journal of Surgery*, vol. 21, April 1, 1959) induced cardiac arrest in adult monkeys by using two salts of potassium citrate: potassium chloride and acetylcholine. The experiments were done in both hypothermic and normothermic animals, after anesthesia was induced with an intravenous dose of thiopental and intratracheal intubation. Cooling was done by immersion and by rubbing ice on the hide, the range of hypothermia varying from 29 to 30 C (84 to 86 F). Cardiac arrest with acetylcholine occurred within a few seconds of administration of the drug. The myocardium retained a certain amount of tone and was not completely flaccid during the arrest. The revival of cardiac rhythm and contraction was easier and more spontaneous than when potassium salts were used. The incidence of fibrillation was less with acetylcholine, and, even if it did occur, it could be easily controlled. An injection of atropine served as an effective antidote, causing a smooth and quick reversion.

The disadvantage of acetylcholine was that the arrest it produced was temporary and often incomplete. This was seen in both hypothermic and normothermic animals. Even as large a dose as 300 mg. did not produce total arrest. The recovery in normothermic animals was even smoother than in hypothermic animals. Fibrillation did not occur in any of these animals. Thus, hypothermia did not offer any added advantage but on the contrary caused minor periods of fibrillation in the recovery phase. The dose of potassium salts varied from 75 to 300 mg., depending on the weight of the animal. The asystole induced by these salts was completely flaccid and absolute, the duration varying from 5 to 19 minutes. Some animals, however, had a definite but variable latent period between the injection and the arrest. Cardiac dilatation and ventricular fibrillation occurred in almost all animals during recovery. The duration and severity of these fibrillatory episodes was much more marked than after acetylcholine, and there was no certain way of terminating them as there was when acetylcholine was used.

Potassium-induced arrest was considered to be of greater help in open cardiac surgery than that induced by acetylcholine, because of the complete flaccidity of the myocardium and the longer duration of the asystole. Its disadvantages were the constant occurrence of cardiac dilatation on releasing inflow occlusion and the development of severe ventricular fibrillation before the return to sinus rhythm. Manual cardiac massage was found useful for treating fibrillation, but it had to be continued for a long time (19 minutes in some animals) before normal rhythm was reestablished. Calcium chloride injection was of doubtful value in treating fibrillation, and coronary infusion of sodium lactate solution was of no value. Hypothermia was of great help in potassium-induced arrest. Of the 11 animals on whom hypothermia was used 8 survived, while survival was rare in the normothermic controls. No brain damage could be detected in the hypothermic animals in whom fibrillation lasted for more than 15 minutes and in whom normal rhythm was ultimately reestab'ished by massage.

In the same issue P. K. Sen and co-workers reported a study on healthy mongrel dogs in which they assessed the action of different cardioplegic agents, alone and in combination. Anesthesia was induced with intravenous administration of thiopental sodium, and positive-pressure ventilation with air by a respiratory pump through an endotracheal tube was used from the start. Inflow occlusion was practiced on all animals before bringing about chemical cardiac arrest. The cardioplegic

drug was injected into the ascending part of the aorta till the heart stopped in diastole. After allowing a certain interval, depending on the type of arrest, various substances were used to wash out the cardioplegic drug, such as whole blood, Ringer's solution, 5% dextrose solution, normal saline solution, and 10% sodium lactate solution. In many animals injections of calcium and epinephrine and cardiac massage had to be resorted to for restitution of heartbeats to normal rhythm. Hypothermia was produced by immersion in an ice-cold water bath when required, the hypothermia being only of moderate depth (about 28 C [82.4 F]).

The various chemical agents tested were potassium citrate alone, acetylcholine alone, combination of potassium citrate and acetylcholine, potassium citrate and acetylcholine under hypothermia, potassium chloride and acetylcholine under hypothermia, and a combination of magnesium sulfate, potassium citrate, and prostigmine. Nine dogs received potassium citrate alone, a 25% solution being used for the first dog, a 10% solution for the next, and a 5% solution for the rest, its amount varying from 250 to 1,250 mg. All the hearts went into ventricular fibrillation during recovery after a diastolic arrest of one to four minutes. Manual cardiac compression and injections of calcium chloride, epinephrine, and occasionally neostigmine were necessary for restitution. Another group of nine dogs received acetylcholine alone. Diastolic arrest occurred within a few seconds but lasted less than a minute. Normal rhythm was restored in all but one who developed ventricular fibrillation. There was no evidence of brain damage in the dogs that survived, the longest survival time being eight days.

Five dogs were injected with acetylcholine and potassium citrate, the former in the same dose as in the second group and the latter in 1% solution in amounts varying from 60 to 100 mg. Diastolic arrest occurred rapidly in all and restitution was started after an interval of two to five minutes. Four animals came back to normal with massage alone, and one required an injection of calcium chloride. Ventricular fibrillation developed in all animals during this process, and it remained permanent in one. The time required for restitution ranged between 4 and 20 minutes and all showed evidence of brain damage. Thirteen animals received the same combination as had the previous group under hypothermia ranging between 30 and 32 C. Diastolic arrest was immediate and was maintained for two to seven minutes. Three animals required intracoronary calcium chloride injection besides massage for restitution, the time required for restitution varying between ½ minute and 20 minutes. Brain damage was definite in two and possible in two others. There were no long-term survivals.

Ten dogs received a combination of 1.2% potassium chloride solution and 2% acetylcholine solution under hypothermia of 30 C. Diastolic arrest was obtained in all within one to four minutes. Six dogs were revived with cardiac massage of one to seven minutes' duration and the remaining four did not respond to either massage or an injection of calcium chloride. Seven developed ventricular fibrillation during restitution. Ten animals were treated with a mixture of magnesium sulfate, potassium citrate, and prostigmine, after induction of hypothermia of 30 C. Diastolic arrest was maintained for two to four minutes in all, but the arrest occurred after a latent period of one-half to two minutes after injection. Seven animals were restored to normal by massage, and some also required an injection of calcium chloride. The time necessary for restitution varied between 2 and 23 minutes. Ventricular fibrillation occurred in only three dogs, one of which was restored to normal after 23 minutes of cardiac massage and an intracoronary injection of calcium chloride. The other two could not be revived.

Thus, of all the agents used, acetylcholine had the most rapid action but the arrest was incomplete and of short duration. Potassium-induced arrest was rapid and complete but recovery was uncertain, often late, and accompanied by ventricular fibrillation. A combination of these two exhibited the balanced action of rapid diastolic arrest of relatively shorter duration but an easier restitution of rhythm. The incidence of ventricular fibrillation was, however, as frequent as with potassium alone. A mixture of magnesium sulfate, potassium citrate, and prostigmine produced a slower but definitive diastolic arrest with the least incidence of ventricular fibrillation and a reversible cardiac standstill.

JAPAN

Artificial Insemination.—According to the *Tokyo Weekly* (May 31, 1959) the Department of Family Planning of Keio University School of Medicine celebrated the 10th anniversary of its successful artificial insemination program. The first child resulting from artificial insemination in Japan, a girl, is in the fifth grade and is bright and pretty. In the past 10 years 300 babies were conceived by this method. Understandably the mothers prefer to remain anonymous. Because of this the director of the department is handicapped in carrying out a complete follow-up study. More than 50% of the mothers ignore questionnaires. After becoming pregnant many mothers prefer to be delivered elsewhere and are lost to the study. In many cases two or three inseminations are required before pregnancy occurs. If after 6 attempts conception does not take place the would-be mothers receive no further encouragement.

The candidates are first referred to the gynecologic department for a potency test, biopsy of the endometrium, and culture of menstrual discharge for tubercle bacilli. If these tests reveal no abnormality, a sample of the husband's semen is examined. If this is found to be deficient in any way both parties are asked to sign a document, separately, giving unqualified consent to the use of the stock sperms. Ovulation is presumed to coincide with the elevation in body temperature of the prospective mother, who is instructed to visit the clinic on the day of presumed ovulation. Reasons given for requesting artificial insemination included the fact that (1) the husband worked in an atomic energy plant and the couple feared damage to his sperms, (2) husband and wife were related and they feared passing on a hereditary disease, and (3) husband and wife were separated but the wife still desired a child of her own. The sperm stocks used were procured from medical students or athletes who received a small fee. Controversies arising from various aspects of this subject have not yet been resolved.

UNITED KINGDOM

Ultrasonic Vibrations.—Because of the danger of exposing the fetus to x-rays, tests are being carried out in the department of obstetrics of Glasgow University to ascertain if the fetal and maternal abnormalities that are detected radiologically at present may be determined by ultrasonic vibrations instead. In most hospitals the number of radiologic examinations during pregnancy is being reduced to a minimum because of the hazards of irradiation to the fetus. Two physicists have been appointed to the Western Regional Hospital Board in Scotland and funds allocated to study the diagnostic uses of ultrasonic vibrations such as have already been used for the diagnosis of abdominal tumors.

Culture of Sarcoid Tissue.—Lundbek and co-workers reported the successful culture of sarcoid tissue from lymph nodes and skin by means of the plasma-clot technique (*Brit. J. Exper. Path.* 40:61, 1959). Lymph nodes from the supraclavicular fossae or skin sarcoids were removed under local anesthesia and cultured in plasma-clot or bovine amniotic fluid enriched with horse serum and bovine or human embryonic extract. Within a few days the tissue fragments were surrounded by a carpet of fibroblasts, which became swollen and enlarged, their chromatin became coarse, and the cells gradually rounded off. These changes were patchy. In nearly all of these patches a number of giant cells developed. Most of the cells contained large eosinophilic cytoplasmic inclusions. These changes were not seen in lymph nodes and skin removed from patients with other conditions associated with lymphadenopathy, such as Hodgkin's disease. The cytoplasmic inclusions could have resulted from the activity of an infectious agent, although this was not proved. Tests are being made to see if these inclusions can be maintained by passage. Attempts to establish transferable cytopathogenic effects with sarcoid lymph nodes and skin in human embryonic lung tissue cultures failed.

Cost of Drugs.—According to the final report of the Hinchliffe Committee the drug bill in relation to the total cost of the National Health Service (NHS) in England and Wales has doubled in the last nine years, despite efforts to curb it. Making allowance for the fall in the value of money, this represents a real increase of about 45% since the fiscal year 1949-1950. While there is no evidence of widespread and irresponsible extravagance in general practitioners' prescribing, there is room for economy. The tendency to order larger quantities of each prescription than are required involved some waste. The cost of the average prescription has risen from 43 to 84 cents, and the average cost of drugs per patient a year has risen from $2.27 to $4.20. No explanation was found for the continuing per capita rise in prescriptions in a period when the improved efficacy of drugs should have shortened the length of illness and returned people to health and work sooner.

The committee recommended that physicians be given more information on prescribing, especially about the costs and advantages and disadvantages of new drugs. They should not prescribe expensive preparations when simpler, equally effective, preparations are available. There should be no ban on the prescribing of new drugs but, until the results of clinical trials are known, doctors should prescribe new drugs only when existing ones have failed. If a given doctor's costs habitually exceed the local average by more than 50% the reason should be sought by the local medical committee. The penalties for excessive prescribing, particularly if a physician prescribes extravagantly to attract patients, should be severe. Some patients exert pressure on their doctors to prescribe particular drugs for them. Posters and notices should be supplied for offices warning patients against "getting the medicine habit."

All medical schools should be encouraged to take an interest in economy in prescribing. More students should spend short periods with general practitioners. There is an urgent need for systematic postgraduate instruction of general practitioners in pharmacology and therapeutics. Every consultant should exercise a proper economy in his own prescribing for hospital patients. Everything possible should be done to prevent public money from being wasted in inflated and expensive sales promotion. The drug industry should be asked to curb the more extreme forms of advertising. New drugs should be subjected to independent controlled

clinical trials as early as possible with speedy publication of the results. One of the committee's chief recommendations was that an advisory body including men with business experience, an economist, and a statistician, be appointed to advise the Minister of Health at an early date on matters affecting drug costs.

Referring to new drugs, the committee said that 18% of all NHS prescriptions in 1950 were for proprietary drugs. This proportion rose in 1957 to just under 50%. In the same period the value of proprietary drugs rose from about 40 to over 67% of the total cost of prescriptions, measured by the cost of ingredients. A recent estimate showed that two groups of drugs, antibiotics and hormones, were together responsible for almost 35% of the total ingredient cost of proprietary preparations.

Doctors Urged to Unite.—British Medical Association leaders urged the 40,000 National Health Service doctors to unite in readiness for a dispute with the government over the report of the Royal Commission on Doctors' and Dentists' Remuneration and any action necessary to back their pay claim. The policy of the 21,000 family physicians was laid down at the annual conference of representatives of local medical committees in London in June. The General Medical Service Committee, which negotiates for family doctors, said: "Under extreme provocation the profession should reserve the right to withdraw from the service." The committee will recommend a total withdrawal of service, with a return to private practice, in the event of an unresolved dispute with the government, but, it warns, that such action would be possible only if the profession was united and resolved to make a stand on principles rather than on matters of remuneration alone.

Hypertension.—A. W. D. Leishman of the United Sheffield Hospital (*British Medical Journal*, May 30, 1959) has followed the progress of 211 untreated hypertensive patients regularly since 1946 and compared it with that of 73 patients treated by lumbodorsal sympathectomy and 118 treated with ganglion-blocking drugs. Half of the untreated patients are dead, and a study of these cases has confirmed that high diastolic pressure, male sex, and the presence of albuminuria or retinopathy are particularly unfavorable features. Changes evident in the electrocardiogram did not appear to influence the prognosis. Rise of blood pressure in untreated patients was uncommon, but in 20 of 176 patients the diastolic pressure increased by 20 mm. Hg. Seven of these developed malignant or accelerated hypertension. This could not have been foreseen when they were first examined. A satisfactory fall in blood pressure was achieved in 80% of the patients who underwent lumbodorsal sympathectomy. The unusual permanence of these results was attributed to extensive dorsal denervation. Ganglion-blocking drugs were given parenterally. Of the patients at present on treatment, 67% were regarded as well controlled.

The treated and untreated groups were judged to have been of equal severity, and comparison of their respective mortality rates was made. Except in malignant hypertension the death rate among treated patients was in no instance appreciably higher than one-third that of the untreated group. Although the length of observation of drug-treated patients was not yet adequate for strict comparison, these figures left no doubt that lives had been extended by both forms of hypotensive treatment. Reduction in the number of fatal strokes was a notable feature. Judged from the fate of untreated patients, the use of ganglion-blocking drugs seemed justified in any person whose diastolic pressure was consistently above 120 mm. Hg, and in the presence of albuminuria it might be advisable when blood pressure was below this level. Hypertensive women, however, did not normally require this treatment unless the diastolic pressure was at least 130 mm. Hg.

M. J. D. Newman and J. I. S. Robertson of St. Mary's Hospital, London, reported in the same issue that they made a survey of 104 patients with initial diastolic pressures over 120 mm. Hg. Most of these patients were treated with ganglion-blocking drugs. The complications occurring were related to the degree of control of the diastolic pressure. In patients with retinal hemorrhages and exudates or papilledema the prognosis was closely related to the degree of lowering of the blood pressure. In those patients with cerebral or cardiac vascular lesions no such relationship could be clearly discerned. Uncomplicated hypertension has a comparatively good prognosis without treatment, and a much larger series would be required to demonstrate any effect of hypotensive drugs.

Cancer Research.—In the British House of Commons, Mr. Sydney Irving asked how much money would be spent by the Minister of Health on cancer research this year. The minister replied that expenditure from public funds on cancer research was mainly undertaken by the Medical Research Council, which expected to spend $1,624,000 for this purpose during the current year, including a grant of $578,000 to the Institute of Cancer Research. Cancer research is also carried out in the National Health Service in the course of treating patients, but it was impossible to make a separate estimate for the expenditure involved. Mr. Irving had nothing but praise for the effort made by voluntary agencies, but he found it hard to understand why, in the attack on this terrible disease, so much of the burden should fall on voluntary effort.

Redundant Consultants.—An annotation in the *British Medical Journal* of June 6 said, with reference to the reinstatement of a dismissed consultant, that the way is now open for belated justice to be accorded to Mr. A. H. Barber, the Oldham gynecologist whom the Manchester Regional Hospital Board wrongfully dismissed in 1952. The Minister of Health has amended the National Health Service Regulations so that now regional boards may offer employment to redundant consultants without creating competition. The new regulations became effective May 27 and apply to Scotland, England, and Wales. After a seven-year battle, which included a successful high court action, repeated pressure on the Ministry by the British Medical Association (BMA) and the Joint Consultants Committee, a campaign in the lay press, and questions in both Houses of Parliament, bureaucratic rigidity and inertia are exposed. It now remains for the Manchester board swiftly to find suitable work for Mr. Barber.

The new regulations go much further than making justice for one man administratively possible. Clause 16 of the Terms and Conditions of Service of Hospital Medical Staff is the only safeguard for consultants against unfair dismissal. It is written into their contracts with regional boards. For a long time the BMA and the Joint Consultants Committee have been imploring successive ministers of health to give substance to their paternal assurances and certainty to their understanding of moral obligation. The new regulations appear to do this. "When as a result of contraction of work or of local reorganization," states the Ministry's explanatory memorandum to hospital authorities, "it becomes, or has become, necessary for a board to terminate the appointment of a consultant or a senior hospital medical or dental officer, the board should first consider whether they can vary his contract and offer him alternative employment. An appointment offered in these circumstances need not necessarily be in the same specialty as the officer's existing post, provided that he has the necessary qualifications for the new post." If the board has no post to offer, and the officer assents, the board should notify all other boards. This is a step toward remedying a serious defect in the terms of employment in the hospital service.

Mammary Cancer.—For many years radical mastectomy, either alone or in combination with radiation therapy, was generally considered the best treatment for operable cases of breast cancer. This, however, has been challenged by McWhirter, of Edinburgh, who advocated simple mastectomy, followed by postoperative irradiation of the axilla, supraclavicular glands, and chest wall for all but advanced cases. Watson has compared the gross five-year survival rates of patients treated by the two methods (*Lancet* 1:1191, 1959). McWhirter's five-year survival rate for 1,882 patients at Edinburgh Royal Infirmary, treated when feasible by simple mastectomy and postoperative irradiation, was 42%. Watson's figures were obtained from the Saskatchewan Cancer Treatment Service, which operates under the auspices of the Canadian government. In the Saskatchewan series 1,055 patients were treated by radical mastectomy and in most this was followed by irradiation. The gross five-year survival rate was 52%. The difference is statistically significant in favor of treatment by radical mastectomy and irradiation.

Athlete's Foot in Children.—The incidence of athlete's foot in school children was studied by English and Gibson (*Brit. M. J.* 1:1442, 1959). Nearly 4,000 boys and girls aged 11 to 14 and 894 boys aged 7 to 10 were examined clinically and mycologically for dermatophytosis. Of the older boys 40% had lesions of the feet and from 6.6% fungi were isolated. The corresponding figures for the younger boys were 33 and 2.2%, and for the girls 30 and 1.6%. The incidence of dermatophytosis increased gradually to the age of 11 and then fluctuated irregularly. Among the children from whom the organisms were isolated 1.5% were symptomless carriers. No correlation was found between infection rate and personal cleanliness, social class, or the use of school showers. By far the most common infecting fungus was Trichophyton mentagrophytes, which caused 84% of the infections. Trichophyton rubrum was responsible for 7.2% and Epidermophyton floccosum for 4%.

There was a close correlation between infection and proximity of the schools attended by the children to swimming pools. It was concluded that the local swimming pool is an important focus of fungal infection. T. mentagrophytes was, in fact, repeatedly isolated from the floors of these pools. The fungus was found more often in pools used by children with a high incidence of dermatophytosis than in those used by children with a lower incidence. Spread in swimming pools was thought to be by infected fragments of skin pressed on the foot while walking over contaminated floors. Members of the swimming pool staff whose duties entailed their entering the water were also found to be infected. Almost continuous cleaning and sluicing would appear to be the only practical ways of preventing infection from these pools.

Infective Hazards of Water Closets.—Experiments made by Darlow and Bale have shown that flushing a wash-down type of water closet can produce a bacterial aerosol of sufficient magnitude to be an infective hazard (*Lancet* 1:1196, 1959). Any process involving splashing or frothing produces droplets, which remain suspended in the air for a variable period, depending on the mass and evaporation rate of the droplets, and the velocity and direction of local air currents. If the liquid con-

tains solid matter in solution or suspension, an aerosol of droplet nuclei will persist after the evaporation of the rest of the droplet, and may be infective. It is not unreasonable to expect that some fecal pathogens can produce infection by inhalation. Furthermore, excreta may contain causative organisms of diseases that affect systems other than the gastrointestinal tract, such as Mycobacterium tuberculosis, poliovirus, and the Coxsackie and ECHO viruses. The authors demonstrated that the flushing of a water closet generates sizes of particles capable of penetrating to the lower respiratory tract as well as of deposition in the nose, mouth, eyes, and on surfaces touched by the hands.

Experiments were carried out with Serratia marcescens as a test organism for the inoculation of an experimental water closet. A sampling apparatus was mounted at varying levels above it. The maximum number of colonies found on the test plates after flushing was 4,000, representing a mean of 2,000 particles and 19,000 organisms per cubic foot of air. The persistence and wide dissemination suggested that many of the particles were small and tended to remain airborne. It was calculated that about 4,500 particles escaped into the room at each flushing. Aerosol formation was not prevented by the use of the weak disinfectants normally employed in the home.

Family Doctor Center.—On June 1 the Family Doctor Center, at Livingstone House, Edinburgh, was opened. Its object is to provide diagnostic facilities for general practitioners in the area, so that they can deal with some patients whom they would otherwise have to send to the local hospitals for diagnosis and, perhaps, treatment. They will be able to bring any patient to the center whom they would like to investigate more fully than their office hours and facilities would normally permit. The center provides a full range of diagnostic facilities. Its use will be restricted to 40 doctors to avoid overtaxing its resources. This number was selected by ballot from over 100 physicians who applied to use the center. If the center is a success others may be built to increase the facilities of doctors in the National Health Service (NHS). The staff consists of an administrative secretary, stenographer, nurse, laboratory technician, medical social worker, radiographer, part-time radiologist, and part-time medical adviser. The center has fully equipped examination rooms, a clinical laboratory, an x-ray room, and an electrocardiograph.

This center should help to remedy one of the defects in the NHS. Many doctors are frustrated because they cannot get tests done on patients without putting them through the diagnostic routine of the big hospital. Often a physician requires only a simple x-ray or a follow-up blood test on a patient, which he cannot get from the hospital except in an emergency, without a long wait. Confirmation of a general practitioner's diagnosis is often delayed for weeks because the patient is referred to a hospital outpatient service, where diagnostic tests may be done at the rate of one a week.

The new center will give the required diagnostic information within a few hours and will provide facilities for the chronically ill, particularly the patient who is mentally ill, or has a multiplicity of symptoms and visits the doctor frequently. Then the medical social workers will be able to help. It is also hoped that the center will bring family doctors together to discuss their diagnostic problems. It is housed in the premises of the general practice teaching unit of Edinburgh University and should thus provide a link between the medical students and general practitioners there.

Temperature of the Brain During Hypothermia.—The safe duration of circulatory arrest in cardiac surgery under hypothermia is limited by the viability of the central nervous system, particularly the vital centers in the brain, the lower the temperature the longer being the time available. The temperature of the brain at the moment that blood flow to it is stopped is the all-important factor in determining the safe period of circulatory arrest. Hitherto, it has been assumed that the temperature of the brain substance is close to that of the nasopharynx or lower third of the esophagus, but this has never been demonstrated.

Hercus and co-workers (*Brit. M. J.* 1:1435, 1959), using an electric thermometer, took simultaneous temperature readings of the rectum, lower third of the esophagus, nasopharynx, right atrium, and cerebral cortex in sheep. A small drill hole was made in the skull to reach the brain, and the right atrium was reached by passing a cardiac catheter through the jugular vein. The body temperature was lowered to 29 or 30 C by immersion in iced water kept at 1 to 2 C. Over the range 29 to 32 C the temperature recorded in the lower third of the esophagus approximated closely to that of the brain. Rectal and nasopharyngeal temperatures did not show such close agreement, as they reflected changes in blood and brain temperatures sluggishly. Under the condition of the test the rectum required 15 to 20 minutes to reach a stable temperature, whereas the central blood, esophagus, and brain temperature became stabilized in five minutes. The aortic blood temperature was always within 0.2 C of the temperature in the lower esophagus. This close correlation between the temperature in the lower third of the esophagus and the cerebral cortex makes it the logical site from which to record the body temperature during operations under hypothermia.

CORRESPONDENCE

THE HOSPITAL SHIP CONSOLATION

To the Editor:—As one who has spent much time in the Far East teaching and helping set up psychiatric work in China, the Philippines, Indonesia, and Thailand (I am returning to Bangkok in November for another four months of teaching at the medical schools there) and as one who has spent the last 38 years teaching psychiatry at Harvard, New York University, and the University of California, where I have taught many doctors from the Far East, I have been much interested in the announcement of the project to spend $3,500,000 to put the hospital ship Consolation into shape and to send a group of physicians, nurses, and public health workers to the Far East, mainly Indonesia.

I would like to register my own feelings about spending $3,500,000 to send this hospital ship to Indonesia. Just lately I heard that two additional ships may be taken out of mothballs next year and sent to the Far East. It is difficult for me to see what lasting good will be accomplished by a project of this sort, whereas it is obvious that the spending of this amount of money to carry out long-term steady work in these places in the Far East would yield many times the good results of sending a hospital ship. It seems possible to me that sending a ship like this may even have the opposite effect from that desired. It is a sort of spectacular grandstand play showing the great wealth and medical facilities of the United States, but how much good actually will be done in the treatment of sick people and how much can thus be done in the way of medical and nursing education in countries such as Indonesia?

For $3,500,000 one could build an excellent medical school with hospital facilities and staff it with teachers for several years—surely something that would have much more lasting value than the hospital ship. I must confess my feeling that this sort of gesture is something that will give emotional satisfaction to some Americans, including many of those participating in the project, rather than do lasting good in Indonesia.

Probably now it is impossible to reconsider and study whether this same amount of money can be used to better advantage in some other project. I do find it difficult to understand why a scheme of this sort should have been rushed into without getting the opinions of some of the doctors who have training and experience in medical work in the Far East and are most qualified to help evaluate what would be the best way to spend such a large sum of money.

Even if it is too late to stop or change this project, it is not too late to plan for a good evaluation of it and to consider carefully the worth of any continuation of this project or the launching of similar ones. Although it seems to me that it would be difficult to estimate the final results of a project of this sort because the native countries and groups involved will be extremely polite and will not openly express any criticisms which they may have, I do believe it is most important that such an evaluation be attempted and that no further projects be activated without an evaluation and a comparison of the use of a hospital ship with other ways the money might be spent.

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To the Editor:—I am delighted to read of the interest and support which the American Medical Association is giving to the "People to People" program between the United States and other countries, but I cannot refrain from voicing some apprehension with regard to the form which this support is taking. I refer to the use of the hospital ship Consolation as a sort of floating medical center and hospital visiting "Southeast Asia." To outfit and run the ship for one year will require $3,500,000.

This amount of money would go far in equipping a permanent medical school, in underwriting visiting teams going over to stay at the medical schools, and in giving advanced training to potential faculty from the foreign country. While perhaps not as dramatic and spectacular, I believe the latter style of educational program would have more lasting effect and in many ways be more acceptable as well as practical.

Except for the health services of the smaller islands (and these needs are now met by our Navy, the British, and the French, as the responsibility lies), a visit by a hospital ship is hardly the best approach for an educational program. From our experience, short, quick visits from American faculty are of little permanent value. I fear it would be little more than a traveling clinic. It could alleviate many of the immediate and acute illnesses but this is a drop in the bucket compared to the over-all health problem presented by the more populous countries of Southeast Asia. Those problems will best be solved by well-trained native health professionals and by long-term investment in education in medicine and public health. At best, the educa-

tional programs under Point IV are too much of an impact phenomenon and do not recognize the need for a slower or sounder approach and maturation.

I believe that the psychological effect of a hospital ship will, on the one hand, tend to separate our visiting group from the host nationals and, on the other, may prove somewhat confining for the morale of the long-term American staff. The matter of language and customs poses many problems in dealing with the sick, whether ambulatory or hospitalized. I am sure it will require much aid from our foreign service personnel. It is conceivable that in some areas it will not be welcome. If I have one suggestion, it is that this well-meaning group consult the China Medical Board or the Rockefeller Foundation before they invest so much money on this type of program.

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FAMILIAL RECURRING POLYSEROSITIS

To the Editor:—The editorial in THE JOURNAL, June 6, 1959, page 678, entitled "Is Familial Periodic Disease a Nosological Entity?," calls attention to a remarkable disease largely limited to persons of the Armenian, Syrian, or Jewish ethnic groups. In support of this concept of a "nosological entity" we should like to bring attention to our study of 20 such patients, presented before the annual session of the American College of Physicians, April 21, 1959. We have added to the nomenclature of the disease "familial recurring polyserositis." The nomenclature of the disease has had interesting historical deviations. First called a "paroxysmal syndrome" by Janeway and Mosenthal in 1908, it was termed "benign paroxysmal peritonitis" by Siegal in 1945. Reimann included it in his collection of periodic diseases and added "periodic abdominalgia" or "periodic peritonitis."

French authors have objected to the connotation of "periodic," and Siguier in 1953 called the disease "la maladie dite périodique" (so-called periodic disease). The attacks do not always recur regularly but often recur at grossly irregular intervals from a few days to several months. Mamou coined the term "épanalepsie Méditerranéene," meaning recurring Mediterranean attacks. Bickel in Geneva reverted to the eponym of "la maladie de Siegal-Cattan-Mamou." In 1955 Heller in Israel added "familial Mediterranean fever." He has based his *sine qua non* for diagnosis on the attacks of fever. We have observed patients without fever during episodes of severe pain associated with serositis of the peritoneum, pleura, or synovia; hence we object to the use of a physical sign (fever) as the title of this disease. We also object to the implication of a geographical predilection in the title of this disease. The familial predilection is to certain ethnic groups rather than to any geographical area. In Lebanon the disease is called simply "Armenian disease."

Perhaps, in the future, further knowledge of the pathogenesis of the disease may reveal a biochemical concept such as the possible relationship of etiocholanolone to periodic fever as described by Bondy. Meanwhile, it is suggested that the term "familial recurring polyserositis" avoids the pitfalls of naming the disease for a geographical area, or a physical sign, and avoids the erroneous connotation of regular periodicity. On the basis of present knowledge, polyserositis most accurately characterizes the clinical nature of this disease with findings derived from involvement of multiple serous membranes, e. g., peritoneum, pleura, synovia, or meninges. Interestingly, no patients have been reported from America with the renal involvement so prominent in foreign reports. We believe that "familial recurring polyserositis" is an autonomous clinical entity and deserves to be removed from the group of so-called periodic diseases.

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URINARY INFECTIONS

To the Editor:—The report by Lattimer and coworkers (THE JOURNAL, June 20, p. 938) on the serious problem of urinary infections due to resistant strains of Aerobacter aerogenes merits attention. In considering the use of kanamycin as a preferred method of therapy in such infections, one must bear in mind the reports of impaired hearing that have been attributed to kanamycin (Lustberg, A., and Hamburger, M., *J. A. M. A.* 170:806 [June 13] 1959; Naunton, R. F., and Ward, P. H.; *A. M. A. Arch. Otolaryng.* 69:396 [April] 1959; and Damuth, H., personal communication).

It therefore seems appropriate to direct the attention of the readers of THE JOURNAL to the study by Hughes and co-workers (*J. Urol.* 80:75 [July] 1958) in which cycloserine appeared to be "of value in the management of chronic urinary tract infection on an outpatient basis, particularly those infections due to A. aerogenes." However, the use of cycloserine, too, is attended with the risk of toxic reactions, a risk which may be minimized with appropriate regulation of dosage.

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MISCELLANY

USE OF HOMOGRAFTS DISPENSED BY CENTRAL ARTERY BANK OF CHICAGO HEART ASSOCIATION

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In August of 1955 the Central Artery Bank of the Chicago Heart Association issued its first lyophilized human vascular segments for transplantation to patients. Under the direction of the cardiovascular surgery committee of the Chicago Heart Association this bank has supplied vascular segments to surgeons throughout the Chicago area for three and one-half years. It is the purpose of this report to review the operations of the Central Artery Bank from Aug. 1, 1955, to Dec. 31, 1958, and to present the results of the use of these grafts in patients.

Three hundred thirty-six homografts have been utilized in patients during this period. All of the vascular segments were obtained at autopsy under carefully controlled conditions. The arteries were sterilized chemically, lyophilized, and stored at room temperature in sealed glass tubes under a vacuum. The methods of obtaining and preparing arterial homografts have been well standardized, and it is not necessary to outline in detail the procedures involved.

With each graft dispensed to a surgeon, a form sheet was attached requesting information regarding the patient, diagnosis, type of operation in which the graft was utilized, and the results of operation. Additional forms were sent to each surgeon at six-month-intervals requesting follow-up information. All expenses of the operation of the Central Artery Bank were borne by the Chicago Heart Association, and the arteries were dispensed without cost to the surgeon, the hospital, or the patient. Special mention is made of the American Red Cross unit in Chicago, which has provided delivery service from the Central Artery Bank to all of the hospitals in which the grafts have been used.

Results in Three Hundred Thirty-six Homografts

The basis of this report is the information obtained from the 38 surgeons in the Chicago area who have used these grafts at operation. The data obtained are presented in categories designated by the type of case in which the graft was used.

Temporary Aortic Cuff.—Fourteen segments of homografts were sutured to aortas to permit inflow from pump-oxygenators and were removed at the end of the procedures, with satisfactory results. None has been used for this purpose since February, 1958, however, and it is likely that the procedure has been discontinued. The principle of using a cuff for access to the aorta may have limited application in certain types of cardiovascular operations.

Roof for Right Ventricle.—One homograft was used for enlarging the right ventricular outflow tract in infundibular stenosis in the period covered by this report. The homograft appears to have certain advantages over the plastic or fabric prostheses for this purpose and will be used in additional similar cases.

Inguinal Hernia Repair.—Two segments of aortic homografts have been used for additional abdominal wall support in two cases of inguinal hernia. The reporting surgeons have indicated that immediate results have been satisfactory and that addition grafts will be used in this manner.

Artery Involved in Tumor.—Three cases of replacement of blood vessels (arteries) involved in tumors have been reported. In two of these cases segments of the abdominal aorta were resected and replaced with homografts. One segment thrombosed one year after operation; the other was reported to be satisfactory at six months, after which the patient was lost to follow-up. In the third case the internal carotid artery was resected and replaced with immediate satisfactory results, but no subsequent reports were received.

Arterial Trauma.—Four cases of resection and replacement with homografts due to trauma to segments of peripheral arteries were reported. Three cases were reported as having satisfactory results with patent grafts up to one year after operation. In the fourth case there was a rupture at the suture line immediately after operation, and the homograft was replaced by a plastic prosthesis.

Superior Vena Cava Obstruction.—Four cases of replacement or bypass of obstructed superior vena cava were reported. In one case of obstruction due

to carcinoma, the patient died two weeks after operation. At autopsy the graft was found to be patent and apparently functioning satisfactorily. In each of the remaining three cases bypass of inflammatory strictures of the superior vena cava was carried out. One graft was patent and functioning well one year after operation. One graft remained patent two years, then thrombosed following an accident. The third graft thrombosed three weeks after operation.

Aneurysm of Abdominal Aorta.—Sixty-one cases of resection of aneurysm of abdominal aorta have been reported. In three cases the segments of aorta including the renal arteries were replaced with homografts. These three patients died in the immediate postoperative period of causes unrelated to the grafts.

Seventeen of the patients with aneurysms were operated on as emergencies for acute rupture. Thirteen of the patients died in the immediate postoperative period, three because of disruption of the proximal suture line. It could not be determined whether these three disruptions were associated with defects in the grafts, faulty suturing techniques, or difficulties with the proximal part of the aorta, although the last possibility is perhaps the most likely.

There were 41 resections of aneurysms involving the aorta below the renal arteries; these patients were operated on electively. There were eight deaths unrelated to the grafts, of which seven occurred in the immediate postoperative period and one occurred 12 months after operation. Three deaths were related to the grafts, all occurring in the immediate postoperative period. One of these deaths was due to thrombosis of the graft with extension of the thrombus into the renal arteries. The other two deaths were due to disruption of the proximal suture line.

Of the patients with aneurysms operated on as emergencies, the four surviving patients are well 6 to 16 months after operation. Of the patients operated on electively, 30 are well 6 to 36 months after operation.

Aneurysm of Thoracic Aorta.—Seven cases of resection of aneurysm of the thoracic aorta were reported. Four of these patients died in the immediate postoperative period of causes unrelated to the grafts. Three patients are well more than 24 months after operation.

Aneurysm of Peripheral Arteries.—Nineteen cases of resection of aneurysms of the peripheral arteries were reported.

There was one aneurysm in a vein graft used to replace the femoral artery. This patient is well nine months after replacement with a homograft.

Two aneurysms of the iliac arteries were resected and replaced with homografts. One of these patients died in the operating room of cardiac arrest. The other patient has been well for 18 months since operation. One patient with an aneurysm of the subclavian artery is well 24 months after operation. One patient with an aneurysm of the axillary artery is well six months after operation.

Five aneurysms of the popliteal arteries were resected and replaced with homografts. One graft thrombosed 18 months after operation. One patient died of a myocardial infarction 18 months after operation with the graft functioning well up to that time. Three patients have been well 12 to 18 months since operation.

Ten aneurysms of the femoral arteries were resected and replaced with homografts. Two of the grafts thrombosed, one at one week and one at three months after operation. One graft ruptured at the proximal suture line. There was one wound infection with subsequent rupture at the proximal suture line. Six patients are well six to 24 months after operation with grafts functioning well.

Coarctation of Aorta.—In 22 cases homografts were used in repair of coarctation of the aorta to bridge the resected segments. Two children with preductile coarctations died immediately after operation of causes unrelated to the grafts.

Of 20 cases of postductile coarctations, two patients died in the immediate postoperative period. One patient died of septicemia, with the offending organism being cultured from the graft at autopsy. The second patient died after rupture of the graft at the site of a focus of bacterial endarteritis. The possibility of contamination of these grafts during the processing has been a cause of ever-present concern. However, cultures are taken routinely and since the bank has been in operation not a single positive culture has been returned. The remaining 18 patients are well 6 to 36 months since operation. This group of patients should be especially valuable for long-term follow-up, since all of the patients are children or young adults in good health.

Transposition of Great Vessels.—Partial correction of transposition of the great vessels with grafts from the inferior vena cava to the left atrium was reported in 71 cases. There were 29 deaths in this group, none of which was related to the grafts. The remaining 42 patients are well from a few weeks to 24 months after operation, with the grafts apparently functioning well in all the patients.

Aortic Bypass, Occlusive Disease.—Forty-one cases of aortic bypass for arteriosclerotic occlusive disease were reported. There were five deaths in this group which were unrelated to the grafts. Thrombosis of one or both limbs of bifurcation grafts occurred in 11 cases, from one week to one year after operation. In 25 cases the grafts have been functioning well from 6 to 36 months after operation.

Aortic Resection, Occlusive Disease.—Fifty-five cases of resection of the abdominal aorta for arteriosclerotic occlusive disease have been reported. There were nine deaths in this group, of which five were not related to the graft. The other four deaths were due to thrombosis of the grafts with extension of the thrombi into the renal arteries. Thrombosis of one or both limbs of bifurcation grafts occurred in five cases, four days to 18 months after operation. Forty-one patients in the group are well with functioning grafts 6 to 36 months after operation.

Resection or Bypass, Occlusive Disease of Peripheral Arteries.—Twenty-seven cases of bypass or resection of peripheral arteries for arteriosclerotic occlusive disease were reported.

There were 10 cases of iliofemoral bypass. In six of these cases the grafts thrombosed from one day to one year after operation. One patient was discharged 10 days after operation with the graft functioning well, but was lost to follow-up thereafter. In three patients grafts are functioning well 15 to 36 months after operation.

There were five cases of iliopopliteal or femoropopliteal bypass. In these five patients the grafts thrombosed, 3 to 12 months after operation.

In three patients segments of the femoral artery were replaced with homografts. Two of the grafts thrombosed, 6 and 15 months after operation. In the remaining patient the graft has functioned well 12 months after operation.

Femorofemoral artery bypass was carried out in nine patients. In seven of these patients the grafts thrombosed immediately or up to five months after operation. In the remaining two patients the grafts have been functioning well 6 and 24 months after operation.

The number of arterial homografts used at operation during the individual years is of some interest. In 1955, 23 homografts were implanted into patients; in 1956, 105 homografts; in 1957, 124 homografts; in 1958, 84 homografts. During the last six months of 1958 only 27 homografts were used. This decrease in demand for the homografts, of course, reflects the increasing preference of many of the surgeons for the synthetic grafts. At present, the greatest demand for homografts from the Central Artery Bank is in the partial correction of transposition of the great vessels. For this procedure the synthetics have not proved to be as satisfactory as the homografts.

It is our opinion that the data presented here indicate that the Central Artery Bank of the Chicago Heart Association has fulfilled the purpose for which it was organized in 1955. Special demands for the homografts continue, and as long as a reasonable number of the grafts are utilized the operations of the bank will be continued. Long-range studies on homografts and on the synthetic fabrics are as yet inadequate, and the final dispositions of both types of grafts are not yet determined.

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STATEMENT OF PRINCIPLES OF ETHICAL DRUG PROMOTION

The Pharmaceutical Manufacturers Association, which was formed in 1958 by the merger of the American Drug Manufacturers Association and the American Pharmaceutical Manufacturers Association, now represents some 140 manufacturers of pharmaceutical products. The board of directors of the Pharmaceutical Manufacturers Association recently adopted the following statement of principles of ethical drug promotion:

We, members of the Pharmaceutical Manufacturers Association, recognizing our responsibilities and obligations to promote the public welfare and to maintain honorable, fair, and friendly relations with the medical profession, with associated sciences, and with the public, do pledge ourselves to the following statement of principles:

1—Prompt, complete, conservative and accurate information concerning therapeutic agents shall be made available to the medical profession.

2—Any statement involved in product promotional communications must be supported by adequate and acceptable scientific evidence. Claims must not be stronger than such evidence warrants. Every effort must be made to avoid ambiguity and implied endorsements. Whenever market, statistical or background information or references to unpublished literature or observations are used in promotional literature, the source must be available to the physician upon request.

3—Quotations from the medical literature or from the personal communications of clinical investigators in promotional communications must not change or distort the true meaning of the author.

4—If it is necessary to include comparisons of drugs in promotional communications, such comparisons must be used only when they are constructive to the physician and made on a sound professional and factual basis. Trademarks are private property that can be used legally only by or with the consent of owners of trademarks.

5—The release to the lay public of information on the clinical use of a new drug or to a new use of an established drug prior to adequate clinical acceptance and presentation to the medical profession is not in the best interests of the medical profession or the layman.

6—All medical claims and assertions contained in promotional communications should have medical preview prior to their release.

7—Any violation of these principles brought to the attention of the President of the Pharmaceutical Manufacturers Association shall be referred by him to the Board of Directors.

These principles were brought to the attention of the Board of Trustees of the American Medical Association at its meeting in Atlantic City. The Board commended the P. M. A. for adopting these principles for ethical drug promotion.

MEDICAL LITERATURE ABSTRACTS

SURGERY

Microscopic Phaeochromocytoma of the Adrenal. P. B. Desai. Indian J. Surg. 21:1-7 (Feb.) 1959 [Madras, India].

The author reports on a 59-year-old man with a microscopic pheochromocytoma in a normal adrenal. The patient was admitted to Tata Memorial Hospital in Bombay, India, because of paroxysmal attacks of headache for one year, unstable blood pressure, pigmentation of the face, and intermittent attacks of vomiting. The blood pressure used to range from 225/135 mm. Hg to 180/100 mm. Hg during the attacks. The basal blood pressure was about 140/80 mm. Hg. An ill-defined round opacity above the left kidney shadow was revealed by a plain roentgenogram of the abdomen. Retroperitoneal pneumography showed a well-rounded shadow, presumably the suspected pheochromocytoma, above the left kidney. The patient was explored by a left-sided thoracoabdominal approach along the 11th rib. Immediate elevation in the blood pressure was observed whenever the left suprarenal area was palpated. A similar manipulation of the right adrenal did not produce any change in the blood pressure. This significant observation led to the decision to remove the left adrenal, although it appeared normal. It was only accidentally discovered that the shadow in the roentgenogram above the kidney region was caused by a cartilaginous patch of thickening on the pleural surface of the diaphragm. The postoperative recovery of the patient was uneventful. The blood pressure showed a sustained drop.

Microscopic examination of the operative specimen showed the distinct contrast between the normal and the tumor tissue of the adrenal. The tumor cells were large with clear cytoplasm, multinucleated, and arranged in cords and sheets, typical of pheochromocytoma. The patient has been followed up for 6 months postoperatively, and he has not had a single attack of headache and rise of blood pressure. His blood pressure now varies from 140 to 160 mm. Hg systolic and from 80 to 90 mm. Hg diastolic. He can, with sufficient reason, be called cured. The significance of sudden elevations of blood pressure, during manipulation of the adrenal gland concerned, in betraying an invisible pheochromocytoma within a seemingly normal and innocuous adrenal, is emphasized. This is a definite indication for removal of that adrenal.

The Treatment of Parosteal Osteoma of Bone. M. M. Copeland and C. F. Geschickter. Surg. Gynec. & Obst. 108:537-548 (May) 1959 [Chicago].

The authors report observations on 22 patients with what they designate as parosteal osteoma, a newly recognized bone tumor which has been designated by others as parosteal osteogenic sarcoma. The new entity occurs in both benign and malignant forms and is seen most frequently in the first 4 decades of life. In 10 of the 22 patients the lesions were found on the posterior surface of the lower femur, bulging into the region of the popliteal space. Similar growths were observed about the upper femur, upper and lower portions of the humerus, upper ulna and radius, upper fibula, and lower tibial regions. The group of patients included 12 females and 10 males. A swelling or mass and local pain or tenderness were the outstanding clinical features. Ten of the patients had noticed a mass for one year or more. One patient had noticed an increasing enlargement of her lower thigh for 7 years. In one patient, irradiation for skin disease preceded the bone lesion by 32 years.

On examination, a mass of bony hardness is felt, which is firmly attached to the adjacent bone. The periphery of the bony mass is usually smooth in contour. On roentgenologic examination, a mass, densely ossified, circumscribed, frequently sharply outlined, and occurring outside the bone but contiguous with it, is usually visible. At operation, the mass is found fused with the periosteum, with pseudoencapsulation often seen at its outer margins. Grossly, on section, the tumor has a firm, dry, striated surface much like fibrosed cancellous bone. Microscopically, although adult bone and fibrous tissue predominate, foci of cartilage cells may be seen. At the periphery the growths are more apt to show increased cellularity and, in a number of cases, have shown features of fibrospindle-cell sarcoma.

Of the 22 cases reviewed, 16 had been previously described by the authors. Observations on these and on 6 new cases emphasize the fact that paros-

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The place of publication of the periodicals appears in brackets preceding each abstract.

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teal osteomas are potentially malignant lesions. The original lesion appeared to be benign in 14 of the 22 patients. Subsequent surgery, necessary for recrudescence, revealed the tumor as benign in only 2 cases at the second operation. The tissue removed in the only or final operation was considered malignant in 15 instances, benign but cellular in 3, and typically benign in 4. Of 18 patients with determinate reports, 11 are living and well 5 or more years after resection (excision) or amputation. Eight of these patients are living and well for from 7 to 25 years after treatment, while 3 lived 5 or more years and then died of metastases. In 8 of 13 patients the disease recurred after local excision or resection, and amputation was necessary. Five of the 8 patients died of their disease, while 3 are living and well after 5 years or more. Three primary amputees are 5-year survivals, without disease.

Ablative surgery by resection or amputation is necessary to cure parosteal osteoma, in the majority of cases. If complete resection in a relatively inactive lesion can be accomplished, cure should result. There is no place for temporizing surgical excisions. If there is any question about adequate en bloc resection, then amputation is indicated. When pathological changes show frank sarcoma, amputation is indicated at once. Recurrent cases, with or without malignant manifestations, are best treated by amputation. Parosteal osteoma must be differentiated from (1) localized myositis ossificans, (2) intraligamentous osteoma or osteoma of the tendon sheath, (3) sclerosing osteogenic sarcoma, and (4) osteochondroma and exostosis. The differentiating features are discussed.

Observations on Hepatitis Associated with Biliary Lithiasis: Histopathological and Clinical Studies on 90 Cases. B. Kourias and N. Papacharalampous. Lyon chir. 55:179-190 (March) 1959 (In French) [Paris].

The authors carried out histopathological studies on liver specimens obtained from 90 patients who had undergone surgery (87 for cholecystitis, with or without lithiasis, and 3 for duodenal ulcer); the object was to find out whether alterations had taken place as a result of the primary disease. The histological examinations were made on both superficial and deep liver specimens obtained by aspiration biopsy. The findings of these examinations showed that there were neither superficial nor deep lesions in 6.9% of the patients, but both superficial and deep lesions were found in 48.8% of the patients. The lesions were severe in 22.7%, moderate in 54.5%, and mild in 22.7%. The deep lesions were much less severe than the superficial ones in 26.6%. The lesions were localized exclusively in the superficial region in 18.6%. Thus, lesions have been found either in the hepatic cells or in the interstitial tissue, or in both, in 93.1% of the patients. The deep lesions should be considered more important than the frequently occurring lesions of the liver cortex. The most serious lesions were noted in patients with jaundice, but no correlation could be established between the duration of the disease and the seriousness of the lesion. A marked inconsistency was observed between the liver function tests in these patients and the extent of the hepatic lesions.

There were 2 deaths. The rest of the patients were followed up for from 1 to 3 years; the results were generally satisfactory even in those who had had severe hepatic disease. This study warrants the conclusion that cholecystectomy or concurrent drainage of the common bile duct will lead to regression of the hepatic lesions in most patients.

Acute Arterial Occlusion of Extremities: Study of 20 Cases. H. M. Coelho, J. Fernandes Oliveira and P. M. Garcia. Rev. paulista med. 54:167-176 (March) 1959 (In Portuguese) [São Paulo, Brazil].

Twenty patients with acute peripheral arterial occlusion were observed during 1957 at the Faculty of Medicine of the University of São Paulo. Observations were made either until death or for more than a year after discharge from the hospital. The period of time which elapsed between the appearance of occlusive symptoms and hospitalization varied between 2 hours and 7 days in 19 patients; in one patient, however, it was 5 months. The occlusion was caused by an embolus in 18 patients, by repeated arterial trauma during intra-arterial blood transfusion in one, and by a dissecting aneurysm of the aorta and right iliac artery in one. Most of the patients who had had rheumatic fever developed embolism between the ages of 40 and 50 years, whereas those with hypertension, arteriosclerosis, and myocardial sclerosis developed it between 55 and 82. The occluded arteries were the axillary in 4 cases, brachial in 3, iliac in 4, femoral in 5, and popliteal in 2, as well as the bifurcation of the aorta in 5. The total number of involved limbs was 28, because of the presence of bilateral or multiple emboli in some cases. Most of the patients were hospitalized in grave condition. Two entered in coma, with severe cardiac disease, multiple embolism, and the legs in cadaveric rigidity; they died of cerebral embolism 5 and 24 hours, respectively, after hospitalization. In the remaining 18 patients there was acute or moderate ischemia in 11 limbs, muscular induration in 5, necrosis in 1, and gangrene in 4. Preoperative treatment consisted of drugs to correct heart decompensation, shock, anemia, dehydration, and decompensated diabetes.

Seven patients had an embolectomy, and arterial circulation was reestablished in the limbs of 5, since the operation was performed within 8 hours after the appearance of occlusive symptoms. An amputation was performed in the case of 3 patients with gangrene; 2 of these patients died. Conservative treatment, consisting of sympathetic blockage and intravenous injections of heparin in doses of 75 or 100 mg. at intervals of 4 hours, was given to 8 patients, with good or fair results in 6; in the remaining 2 patients the treatment was followed by the appearance of gangrene, which called for amputation. Of the 20 patients in this series, there was an operative mortality from embolectomy or amputation in 4 patients, and death occurred as a result of embolism or gangrene in 7. Nine patients are surviving in a satisfactory or fair condition one year after discontinuation of the treatment. The best results were obtained in those who were treated not later than 8 hours after the appearance of occlusive symptoms.

Needle Biopsy of the Liver During Abdominal Surgery. R. B. Terry. Am. J. Digest. Dis. 4:378-388 (May) 1959 [New York].

The author describes an instrument which has been found suitable for needle biopsy of the liver during abdominal surgery. In patients with abdominal carcinoma in whom hepatic nodules are found, liver biopsy becomes imperative. Such hepatic nodules are often difficult to assess by inspection and palpation. In a proportion of cases unnecessarily palliative surgery may be performed, and gross errors in prognosis made, if hepatic nodules are not examined histologically. Biopsy of the liver by wedge resection during abdominal surgery is occasionally attended with difficulty and may fail to obtain satisfactory tissue because of the atypical nature of the free margin of the liver; for these and other reasons, it is frequently not performed when indicated. Needle biopsy of the liver during abdominal surgery is simple and rapid; any bleeding is easily controlled, and the specimen obtained is not only adequate in size but contains fewer artefacts than that obtained by wedge resection. The author performed 35 biopsies with the biopsy instrument during abdominal surgery. The material proved to be adequate for diagnosis. There was no difficulty in controlling bleeding, which in many instances was remarkably slight, and no complications were encountered in the series. The mortality rate for "medical" or percutaneous biopsies of the liver has been 0.12% among 10,600 biopsies reported in the literature, while the incidence of significant complications has been 0.38%. There would presumably be far less trouble with needle biopsy of the liver performed during abdominal surgery.

GYNECOLOGY & OBSTETRICS

Endometriosis Involving the Pleura. C. B. Ripstein, M. Rohman and J. B. Wallach. J. Thoracic Surg. 37:464-471 (April) 1959 [St. Louis].

The authors report on a 24-year-old woman with endometriosis involving the pleura. The patient had recurrent hemorrhagic effusion, increased menses associated with moderate abdominal pain, and inability to conceive. The diagnosis was considered clinically and was confirmed by histological examination of tissue from the pleural and peritoneal cavities. Diagnostic pneumoperitoneum was followed promptly by pneumothorax, indicating the presence of a communication between the pleural and peritoneal spaces on the right and permitting the application of the implantation theory in explanation of this unusual site of endometriosis. The cases of only 2 patients with pleural endometriosis and 1 with endometriosis of the lung have so far been reported in the literature. This pathological process should be considered in a young woman with recurrent hemorrhagic pleural effusion of obscure etiology. Early treatment directed at suppression of ovarian function will provide relief of the debilitating symptoms secondary to the continuing accumulation of the irritating bloody fluid in the pleural space.

Combined Radiologic-Surgical Treatment of Carcinoma of the Cervix. T. Dahle. Surg. Gynec. & Obst. 108:600-604 (May) 1959 [Chicago].

The author believes that both irradiation and surgical treatment have a place in the therapy of carcinoma of the uterine cervix. This study was undertaken to investigate the anatomic spread of cancer of the uterine cervix in patients with stage 1 lesions, and to analyze the dangers to the ureters in combined radiologic and surgical treatment. Two hundred sixty-six patients with stage 1 cervical cancer were admitted to the Norwegian Radium Hospital in Oslo in 1954, 1955, and 1956. For various reasons it was not possible to perform radical surgery on all these stage 1 patients, and only 96 of them underwent radical surgery and preoperative radium treatment. The material was a selected one, the patients being young and in relatively good condition. The clinical staging was always made under Nembutal anesthesia, and the examination of the renal tract always included urinalysis, determination of the blood urea, cystoscopy, and urography. There were 88 cases of squamous-cell carcinoma and 1 of adenocarcinoma; in 7 cases the diagnosis was undifferentiated carcinoma.

All the patients first received radium treatment equivalent to from 6,000 to 7,200 mg.-hr. in 1 or 2 fractions (30 mg. of radium in the vagina and 20 to 30 mg. in the uterus for 5 days). The patients selected for combined therapy were discharged for

6 to 8 weeks and then readmitted for radical hysterectomy and pelvic lymphadenectomy. The patients not selected for the combined treatment, immediately after the radium treatment, underwent a complete course of x-ray therapy, including a 3,000-r skin dose to each of 2 anterior and 2 posterior pelvic ports. It is known that the clinical staging of patients with carcinoma of the cervix is often unreliable, and such was the case in this material. In 18 of the 96 supposedly stage 1 patients, metastases were found in the lymph nodes. Since Meigs found lymph node invasion in 17.5% of stage 1 patients treated only surgically, it appeared that radium therapy had no influence on the lymph node metastases. In 16 of the 96 patients, residual carcinoma was found in the cervix, but in 12 of the 18 patients with lymph node metastases, no residual carcinoma was found in the cervix.

No rectovaginal or vesicovaginal fistula resulted, but, when possible, damage to the ureters was examined by means of urography; 69 patients showed no abnormality from 6 months to 1 year after treatment, but 22 did show damage. Four patients are now dead, 3 having died of carcinoma and 1 of bilateral pyonephrosis. It is believed that most of the changes in the urinary tract were caused by the treatment, but in 11 of the patients the hydroureter or hydronephrosis was slight. The possibility of damage to the urinary tract must be borne in mind when reflecting on the value of the combined radiologic and surgical treatment.

Association of Cervical Cancer with Circumcision of Sexual Partner. J. E. Dunn Jr. and P. Buell. J. Nat. Cancer Inst. 22:749-764 (April) 1959 [Washington, D. C.]

There have been reports to the effect that cervical cancer is only one-fifth or less as frequent in Jewish women as in non-Jewish women. Wynder and associates in 1954 reported on data from 2 sources in support of the hypothesis that circumcision of the male is a protective factor. The present authors suggest that other factors might be involved. They present data from a study not designed solely to test the question of circumcision but to study other variables possibly associated with cervical cancer. During the years 1951-1955, 429 patients with cervical cancer were interviewed. The same number of controls were selected by matching on age (within 5 years), race, ever married, and ever parous. A further restriction was made by selecting the patient-control pair from the same hospital (Los Angeles County Hospital) or the same private or group practice. Attention is called to differences in the collection of controls by Wynder. The present authors in their interviews were unable to find an association between having cervical cancer and reporting an uncircumcised husband. Wynder had previously reported an association in a study that also used data on circumcision history obtained from interviews with women patients. There may have been differences in asking the questions about circumcision, but, if so, it is not clear how the data were affected.

An additional independent investigation of circumcision as an anatomic fact revealed that Jewish men probably have a maximum degree of anatomically complete circumcision, which occurs in less than half of non-Jewish men who consider themselves circumcised. The circumcision study also revealed that one-fourth to one-third of men naturally may have a partially shortened foreskin, which is similar to that of some men who have been circumcised, but, in an interview study, many of them will be counted as uncircumcised. Consequently an interview study of non-Jewish subjects may fail to identify the fully circumcised and further dilute the results with many "partially circumcised" classified as uncircumcised. Possibly the problem can be settled only in a study which makes direct examinations of sexual partners to distinguish full and partial circumcision.

The Occurrence of Episodes of Immunization in Pregnancy Associated with Rh Haemolytic Disease of the New-Born. G. A. Kelsall, G. H. Vos and R. L. Kirk. M. J. Australia 1:488-493 (April 11) 1959 [Sydney].

The authors carried out antenatal titrations of antibodies found in pregnant mothers, serums at the King Edward Memorial Hospital for Women in Subiaco, Western Australia, at every available opportunity during the last 7 years. Frequent titrations in the course of pregnancy showed that immunization of the mother occurs as one or more episodes during the pregnancy, and that the resulting antibody titers may be of minor or major magnitude. The prognosis for the fetus depends largely on the Rh-antibody titer. The patterns of antibody behavior were numerous and varied. The findings seem to justify the following conclusions concerning the prognosis for a particular pregnancy and the outlook for later pregnancies. 1. A previously immunized woman may undergo a further incompatible pregnancy without any episode of immunization occurring in the later pregnancy. If the initial titer in such a pregnancy is low, the infant will be mildly affected; if the initial titer is high, the infant may be severely affected. 2. A previously immunized woman may have one or more episodes of immunization in a subsequent incompatible pregnancy. The outcome for the fetus will depend on the number of episodes, the rise of titer, and the duration of a high titer of antibodies. 3. Antibody titers may fall between pregnancies, and sufficient time must be allowed for this to happen. A sensitized woman mated to a homozygous man has a much better chance of having a surviving infant if her titer is low at the beginning of pregnancy.

Antibodies frequently appear for the first time in the last 4 weeks of pregnancy, and they may rise precipitiously to lethal levels in the few remaining weeks of pregnancy. Of 409 immunized mothers, 75 (18%) were free of antibodies when first examined by the authors; antibodies developed in 33 (8%) before 34 weeks of gestation had been completed, and in 42 (10%) antibodies developed after this time. Of the 334 (72%) who already had antibodies when first examined, 113 (25%) had an episode of immunization before 34 weeks, and 198 (45%) had one after 34 weeks' gestation. The premature induction of labor at 36 weeks probably obviated the occurrence of many more dangerous episodes in the last 4 weeks of pregnancy. Induction of labor is not only of value in that particular pregnancy, but must have some bearing on the success of future pregnancies, in that it would tend to keep the mother's titer at a lower postconfinement level and provide a lower antibody "take off" when the next pregnancy begins.

Wertheim Hysterectomy in the Treatment of Endometrial Carcinoma. L. Parsons and F. Cesare. Surg. Gynec. & Obst. 108:582-590 (May) 1959 [Chicago].

In view of the renewed interest in radical dissection of the pelvic lymphatics for cervical cancer, the authors elected to employ the Wertheim type of hysterectomy and pelvic node dissection in the treatment of endometrial carcinoma. This report, based on 62 cases in which treatment consisted of the Wertheim hysterectomy, is presented as a critical study of the many factors underlying the management of endometrial carcinoma by a radical surgical approach. The patients were observed at several hospitals in the area of Boston between 1946 and 1956. There were 52 adenocarcinomas, 9 adenoacanthomas, and 1 carcinosarcoma. Fifty-two were primary cases, while in 10 previous irradiation had been received. Myometrial invasion was present in 37 cases, or 60% of the group. Bilateral pelvic lymph node dissection was carried out in 50 of the 62 patients, while in the remaining 12 no pelvic lymph node dissection was done. Lymph node involvement was observed in 4 of the 50 patients in whom the nodes were dissected, and these 4 belonged to the group of 37 who had myometrial invasion. One of the 4 women died in the hospital, 1 lived 3 years, and 2 are alive and well at 2 years. Complications occurred in 27% of the patients, urinary tract disturbances accounting for 12% of these. Urinary fistulas developed in 5 patients, an incidence of 8%. Etiological factors as well as practical preventive measures are discussed. There was one surgical death (1.6%).

The technique of the Wertheim hysterectomy is briefly described. Of 3 pelvic recurrences, 2 appeared within the first year, but the third not until 3 years after the operation. This latter case is of special interest, having shown both myometrial and lymph node involvement. Two of these patients ultimately died of their disease, while the third is still living and well 6 years after vaginectomy. The 5-year survival can be evaluated in 33 of the 62 patients. Twenty-six of the 33 patients survived 5 years or more without recurrence, an absolute 5-year cure rate of 78%. Two patients are now alive and well 10 years after surgery. The 5-year survival of the primary treatment group was 81% (22 of 27 patients). In the patients with myometrial invasion the 5-year salvage rate was 71%.

The authors feel that the results obtained compare favorably with those reported in the current literature and justify further evaluation of the radical surgical approach for the treatment of endometrial cancer. The high incidence of postoperative complications, however, imposes heavy obligations on those who treat and care for these patients. It is hoped that future experience and observations will add to the knowledge of the metastatic spread of endometrial cancer, improve selection of patients, and reduce morbidity, at which time the Wertheim hysterectomy with pelvic lymph node dissection may prove worthy of more routine use.

Early Cancer Detection: Prediction of Preclinical and Preinvasive Stages by Cytology. J. E. Ayre. Acta Unio internat. contra cancrum 15:289-295 (no. 2) 1959 (In English) [Louvain, Belgium].

In the diagnosis of early preclinical cancer, cell scraping is the method of choice for the collection of material. In examinations on 111,963 patients, 1,874 gynecologic cancers (20.3%), were found by cytology, and 59 were missed, including 22 cervical cancers. Absence of clinical symptoms is inadequate in discarding cancer diagnosis. Comparisons of clinical appearance and cytological findings are presented for preinvasive, early invasive, and infiltrating cancers. Among 347 histologically confirmed cancers, 70 were "cytologically early"; cytological diagnosis of preinvasive nature was confirmed in 70% of the cases. Cell-population studies allowing this diagnosis are discussed.

PEDIATRICS

Sequestration of the Lung. M. C. Buchanan. Arch. Dis. Childhood 34:137-139 (April) 1959 [London].

The author reports on a girl with an abnormal pulmonary artery supplying a sequestrated segment of the lung, who at the age of 8 years was admitted for the first time to the Queen Elizabeth Hospital for Children in Londan for vague symptoms of ill health, such as tiredness, occasional headaches, pain in the limbs, and cough. A chest roentgenogram did not show any evidence of a pulmonary

lesion except basal emphysema on both sides. At the age of 11 years the patient was again admitted to the hospital for similar symptoms. In addition, her temperature was 103 F (39.4 C). A chest roentgenogram showed a partial collapse of the right middle lobe and the anterior segment of the lower lobe. Sulfonamide and penicillin therapy was ineffective in controlling the symptoms and the pyrexia. Improvement resulted from treatment with chlortetracycline (Aureomycin), and serial chest roentgenograms showed some resolution of the lesion at the right base, but a tomogram showed cyst-like cavitation in the periphery of the right lower lobe, irregular consolidation, and thickening of the bronchial wall.

After 13 weeks in the hospital, the patient was discharged, only to be readmitted 3 weeks later with anorexia, recurrence of cough, and a temperature of 100 F (37.8 C). A bronchogram was obtained, revealing a lesion whose behavior, site, and appearance suggested a sequestrated lung segment. Excision of the right lower lobe was performed. There was a small mass in the posterior basal segments. Entering this mass from the region of the diaphragm was a vessel about 3 mm. in diameter. Microscopic examination of the operative specimen revealed a small abscess cavity in the posterior subapical area. In the posterior basal region there was an area of lipid pneumonitis containing a number of small abscesses. In the anteromedial portion of the lobe there was a tube-like structure which extended laterally and divided into a number of branches; this was thought to be an ectopic bronchus. Moreover, there was emphysema of the basal segments. After the operation the patient made a complete recovery.

The syndrome of sequestrated lung segment is probably not as rare as is generally believed. The condition is disabling, but it is cured by surgery. There are few symptoms referable to the lungs, minimal physical signs, but gross roentgenologic changes. The condition, once suspected, can be diagnosed before operation. The most likely explanation of its causation in the patient reported is that there was a small communication between the air contained in the surrounding normal lung and the air spaces in the ectopic tissue; this was sufficient to aerate the latter, but it was insufficient to drain the products of infection once the condition had occurred.

Treatment of Diphtheria with Terramycin. H. W. A. Voorhoeve. Maandschr. kindergeneesk. 27:119-132 (April) 1959 (In Dutch) [Leiden, Netherlands].

The incidence of diphtheria has decreased in the Netherlands in recent years, and this has been ascribed to the fact that more children are being vaccinated against it. The mortality of diphtheria, however, has remained about the same, namely, 6%. This persisting high mortality induced the author to evaluate the treatment of diphtheria. He compared 2 groups of 55 patients each, one being treated before 1953 and the other after 1953. The diagnosis was bacteriologically verified in both groups of patients. All were treated with the same type of antidiphtheria serum, which was administered by intramuscular injection in doses of from 20,000 to 40,000 units.

On the basis of a 1953 report by Lall and Karelitz, of New York, on the use of Terramycin in diphtheria (abstracted, J. A. M. A. 153:592 [Oct. 10] 1953), the administration of Terramycin, in addition to antidiphtheria serum, was begun at the Juliana Kinderziekenhuis (Den Haag) in October, 1953. Terramycin was given in daily doses of 50 mg. per kilogram of body weight, divided into 3 or 4 doses, usually by mouth. While the addition of Terramycin to the treatment produced no noticeable change in the mortality from diphtheria, throat cultures became more rapidly negative, so that the children did not have to remain isolated for such a long period and hospitalization could be shortened. On the other hand, it seems probable that with Terramycin therapy the immunizatory effect of the diphtheria is lessened, and so the author feels that patients who have received Terramycin for diphtheria should still be immunized against the disease.

The Antibiotic Management of Staphylococcal Disease in Infants and Children. M. D. Yow, M. M. Desmond and L. N. Nickey. South. M. J. 52:392-400 (April) 1959 [Birmingham, Ala.].

The authors report on 155 infants, aged less than 2 months, 32 babies, between the ages of 2 months and 2 years, and 17 older children, all with staphylococcic infections who were treated with antibiotics at Jefferson Davis Hospital in Houston, Texas, between 1956 and 1958. Eighty per cent of the staphylococcic infections were classified as hospital-acquired, and 20% were considered to be of extra-hospital origin. Sixty-six of the 204 patients had mild disease, and 138 had moderately severe or severe involvement. The antibiotic agents employed were selected on the basis of probability of response until the results of in vitro testing were available. During the first year of this study most of the patients with hospital-acquired infections were treated with a combination of erythromycin and streptomycin, erythromycin and chloramphenicol or chloramphenicol or novobiocin alone (bacteriostatic antibiotics). Disappointing results with these commonly used antibiotics and increasing awareness that a large proportion of these infections were due to the virulent Staphylococcus organisms phage-type 81, led to a trial of bacitracin and kanamycin (bactericidal agents). Both these drugs seemed especially suitable for use in infants and children because of their bactericidal activity

and because they could be administered by the intramuscular route. In seriously ill patients all antibiotics were given initially by the parenteral route for a minimal period of 48 hours. Oral therapy was used when the patient began to improve and where it was practical. Local administration of antibiotics was used in localized infections, such as empyema, purulent pericarditis, meningitis, and septic arthritis.

The age of the patients influenced morbidity and mortality. Among the 138 patients with serious staphylococcic disease, the mortality rate was 43% in the premature infants, 26% in the full-term newborn infants, 21% in children from 2 months to 2 years of age, and 12% in older children. The degree of dissemination was related to the age of the patient, demonstrating inadequacy of host defenses in the young infant. The selection of the specific antibiotic agent for the treatment of staphylococcic disease, including impetigo, conjunctivitis, subcutaneous abscess, septicemia, pneumonia, gastroenteritis, meningitis, and miscellaneous conditions, depends on the age and condition of the host. In older children or patients with normal defense mechanisms, mild and moderately severe staphylococcic infections can be expected to respond to treatment with bacteriostatic antistaphylococcic drugs. Controlled studies are needed to establish the best method of management of mild superficial infections in the newborn infant. Even moderately severe infections in the young infant must be considered potentially dangerous because of the infant's inability to localize infection, and this patient should be treated with a bactericidal antistaphylococcic drug. The prognosis of severe staphylococcic disease in all age groups is so grave that intensive therapy with a bactericidal antibiotic or a combination of a bactericidal drug and a bacteriostatic drug is indicated.

Nephrocalcinosis Infantum. R. A. Shanks and A. M. MacDonald. Arch. Dis. Childhood 34:115-119 (April) 1959 [London].

The authors report on 84 cases of nephrocalcinosis observed in children who died at the Royal Hospital for Sick Children in Glasgow and on whom autopsies were performed between 1928 and 1957. Nine cases were observed between 1928 and 1937, 15 between 1938 and 1947, and 60 between 1948 and 1957; these data suggest a true increase in the incidence of this condition. Of the 9 cases, 3 occurred in infants aged less than 1 year, 1 in an infant between 1 and 2 years, and 5 in children over 3 years of age. Of the 15 cases, 9 occurred in infants aged less than 1 year, 3 in children between 1 and 3 years, and 3 in children over 3 years of age. Of the 60 cases, 47 occurred in infants aged less than 1 year, 10 in infants between the ages of 1 and 2 years, and 3 in children over 3 years of age. Thus, 70% of the cases were observed in infants in the course of the first year of life.

A wide variety of pathological conditions, in themselves sufficient to cause death, was found in association with the lesions of nephrocalcinosis in this series of patients. The first and most obvious explanation for these findings is that nephrocalcinosis is a casual autopsy finding seldom related to the cause of death. The virtual absence of the condition in children between 2 and 3 years of age likewise suggests that not only is it usually not fatal but it normally proceeds to complete resolution. The implications, therefore, are that most of the lesions of nephrocalcinosis belong to a benign disorder of infancy without severe symptoms and with an excellent prognosis. The condition is probably related to idiopathic hypercalcemia of infancy.

OPHTHALMOLOGY

The Treatment of Iris Melanoma. A. B. Reese and G. W. Cleasby. Am. J. Ophth. 47:118-125 (May) 1959 [Chicago].

This report is based on 157 cases of melanoma of the iris. They include (1) patients seen and treated at the institute of ophthalmology, Columbia-Presbyterian Medical Center, New York, and Stanford University Hospital, San Francisco; (2) patients seen in consultation by members of the staff of the institute of ophthalmology but treated elsewhere; and (3) patients operated on elsewhere, whose tumor specimens or sections were sent to the pathology department of the institute of ophthalmology for opinion. From the standpoint of treatment the 157 patients fall into the following 3 groups: (1) those that had excisional iridectomy (63); (2) those that had enucleation (72); and (3) those that were observed (22). Patients in the third category were those who were thought to have a probable malignant melanoma based on clinical appearance and behavior but who either refused operation or were not urged to have surgery.

Any pigmented iris lesion showing progressive growth or other evidence of malignant behavior should be excised by means of iridectomy if it seems possible to remove it completely in this manner. A lesion located in the periphery of the iris should be excised early, since any growth would be likely to involve the angle and ciliary body. Enucleation is advisable if the tumor has obviously spread beyond the reach of local excision or there is evidence of residual tumor peripheral to a previously performed iridectomy. The pathological diagnosis of malignant melanoma does not provide grounds for enucleation in the absence of microscopic and/or clinical evidence of remaining tumor. Observation is necessary in any case in which there is not clear-cut evidence of malignant character or behavior, and there are no other indications for surgery.

The over-all mortality in this series, as in other groups reported, was quite low. There were 4 known deaths due to metastatic spread in the 140 cases with follow-up information. Altogether, 60 cases have been followed for 5 years or longer, and 120 cases for 2 years or longer. Of great importance is the fact that no deaths occurred in patients receiving excisional iridectomy as the definitive therapy. It is evident that an iridectomy performed properly at a time when all the tumor can be removed in this manner not only prevents metastatic involvement but avoids the late complications of secondary glaucoma, pain, and blindness which can result from local dissemination. Analysis of the 4 fatal cases shows that enucleation was ultimately performed in each instance. In all these cases microscopic study revealed that the tumor had spread beyond the reach of local excision. In 2 cases excisional biopsies were performed 6 days and 1 week, respectively, prior to subsequent enucleation. In the third case, iridectomies were performed in the course of 2 trephining operations during a 5-month period prior to enucleation, when it was ultimately recognized that the glaucoma present was secondary to a diffuse melanoma of the iris. In the fourth case enucleation was performed without initial iridectomy.

External Ophthalmoplegia as Part of Congenital Myasthenia in Siblings: Myasthenia Gravis in Children: Report of a Family Showing Congenital Myasthenia. F. B. Walsh and W. F. Hoyt. Am. J. Ophth. 47:28-34 (May) 1959 [Chicago].

The authors describe observations on 4 boys with congenital myasthenia and external ophthalmoplegia, who belonged to a family of 6 children in which the parents and 2 daughters were normal. They discuss the various types of myasthenia in children, pointing out that congenital myasthenia is a term used by Levin to describe a form of myasthenia which begins at birth (or before) and is characterized by a mild onset, marked external ophthalmoplegia, partial ptosis, and symmetrical weakness of involved muscle groups. It may be associated with marked weakness of skeletal muscles, especially neck, trunk, and leg muscles. In contrast to the usual form of myasthenia gravis, it is not progressive, does not have remissions, and may improve with time, the response to Prostigmin being dramatic. This disease occurs in siblings without involvement of the parents and is variable in severity. Levin feels that it is not the myasthenia gravis described by Erb and Goldflam, though the basic defect (dysfunction at the myoneural junction) is the same or at least is similar.

The 4 cases presented by the authors closely resembled those described by Levin. Partial ptosis and almost total external ophthalmoplegia were the outstanding findings. One member of this family had severe generalized weakness and fatigability of his skeletal musculature, which was symmetrical and which showed neither remissions nor improvement with time. The response to Prostigmin, though, was dramatic. The use of Prostigmin and electromyography is urged in the differential diagnosis of congenital external ophthalmoplegia.

Arcus Senilis: Its Pathology and Histochemistry. D. G. Cogan and T. Kuwabara. A. M. A. Arch. Ophth. 61:553-560 (April) 1959 [Chicago].

Arcus senilis consists of a peripheral corneal opacity that depends on the presence of proximal blood vessels but yet spares the immediate surroundings of the blood vessels. While present to some extent in all persons past middle age, an arcus is also present occasionally in young persons and is particularly common in persons with familial hypercholesteremia and xanthomatosis. A histological study of 25 eyes obtained through the facilities of the Boston eye bank revealed that arcus senilis is characterized by a hyaline sudanophilia of Descemet's and Bowman's membranes and a granular sudanophilia of the corneal stroma. It is invariably associated with a similar sudanophilia of the anterior sclera. The sudanophilia of Descemet's membrane is noteworthy in that it tends to spare the most peripheral portion of this membrane, and, in its early stages, it involves preferentially the anterior half of this membrane in the form of double laminas. The sparing of the limbus is apparently due to the vascularity of this region. Histochemical and solubility studies of sections from these eyes were performed with the purpose of identifying the fat of arcus senilis. It appeared to be a mixture of cholesterol, phospholipid, and neutral fat. The facts that it may be present in relatively massive amounts, and that it does not depend on any degenerative change in the cornea, suggest that it is derived from the blood and becomes secondarily bound to the tissue. The authors, though, were unable to induce any similar binding in vitro by a comparable mixture of lipids from egg yolk.

THERAPEUTICS

Effect of Drugs on Motion Sickness Produced by Short Exposures to Artificial Waves. E. M. Glaser and R. A. McCance. Lancet 1:853-856 (April 25) 1959 [London].

The authors tested the effectiveness in the prevention or treatment of motion sickness of 4 drugs, hyoscine hydrobromide (in doses of 1 mg.), cyclizine hydrochloride (in doses of 50 mg.), meclizine hydrochloride (in doses of 25 mg.), and perphenazine (in doses of 8 mg.), as well as a lactose placebo; the subjects were 77 soldiers, between the ages of 19 and 25 years, who volunteered for the tests. For an

hour after the capsules containing the drugs had been taken, the persons tested were exposed to motion in inflatable tended rubber floats, the position of which in an experimental tank varied from test to test. While exposed to wave motion, the persons were asked to sit up in order to have constant and maximal stimulation of the vestibular apparatus. In the cross-over-double-blind experiment, hyoscine hydrobromide gave significantly better protection against sea sickness than the other treatments. Cyclizine (Marezine) hydrochloride provided somewhat better protection than the undistinguishable lactose placebo. Two commercial preparations of meclizine hydrochloride, Ancolan and Bonamine, as well as perphenazine (Trilafon), were not more effective than the lactose placebo. In single exposures, the lactose placebo appeared to provide significant protection from motion sickness when compared with the effects of no treatment at all. Divergent findings in different experiments could be explained by the possibility that the apparent effects of drugs against motion sickness are sometimes due to psychological reasons, and that the effects of treatment could also be related to the varying susceptibilities of the persons to motion sickness.

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Experiences with Isolation-Perfusion Technics in the Treatment of Cancer. O. Creech Jr., E. T. Krementz, R. F. Ryan and others. Ann. Surg. 149: 627-640 (May) 1959 [Philadelphia].

In an attempt to administer effective amounts of cancericidal agents and at the same time reduce the danger of systemic toxic effects, the authors developed the isolation-perfusion techniques for the treatment of malignant lesions. These techniques consist in excluding the tumor-bearing area from the systemic circulation and perfusing it with a chemotherapeutic agent. For tumors on the foot and leg without evidence of inguinal spread, perfusion is accomplished through the common femoral artery and vein. For perfusion of lesions of the hand and forearm, the proximal portions of the brachial artery and vein are used. Exclusion of the lungs is accomplished with the use of 2 extracorporeal circuits. Heart-lung bypass is employed between the venae cavae and the femoral artery, while in the pulmonary circuit blood from the left atrium is routed through a pump oxygenator and returned to the pulmonary artery by gravity. In perfusing lesions within the pelvis, pneumatic tourniquets are placed in the upper portion of both thighs, and the abdominal aorta and inferior vena cava are cannulated near their bifurcation, either directly through an abdominal incision or indirectly by passing catheters through the common femoral artery and vein. Cannulation in the breast is accomplished through the subclavian artery and vein which are reached through the supraclavicular area. For patients whose disease is not regionally confined, a method of perfusing the entire body for treatment of disseminated tumors has been developed also.

During the past 1½ years 73 patients with malignant tumors have been treated with chemotherapeutic agents administered by these techniques. Of the 73 patients, 37 had carcinoma, 18 had sarcoma, and the remaining 18 had melanoma. The chemotherapeutic agents employed were nitrogen mustard, phenylalanine mustard, actinomycin-D, triethylene thiophosphoramide, and 5-fluorouracil, a pyrimidine analog. Of the 73 patients, 56 were treated for palliation of far-advanced malignant lesions, and 17 were perfused in conjunction with extirpation of the primary lesion. Thirteen patients have died. Of the 60 surviving patients, 22 are well, and the lesions appear to be controlled; in 8 the disease is quiescent; and 30 have recurrences. The results obtained suggests that some human cancers can be controlled with chemotherapeutic agents administered in high concentration, but that great variations exist in the response of malignant tumors to these agents. The factors contributing to the response of a malignant tumor after administration of a chemotherapeutic agent by the perfusion technique are not clear. By affording a means for in vivo investigation of tumors in man, the isolation-perfusion techniques may contribute to the understanding of malignant lesions, and ultimately to better therapy.

New Method for Control of Anticoagulation Treatment. P. A. Owren. Tidsskr. norske lægefor. 79:375-379 (April 1) 1959 (In Norwegian) [Oslo].

The new test for control of anticoagulation therapy is about equally sensitive to variations in each of the 4 clotting factors which are reduced during anticoagulation treatment – prothrombin, proconvertin, Stuart Prower factor, and antihemophilic-B factor. The "all-in-one" reagent applied contains an active cephalin-lecithin preparation and a weak thromboplastin reagent, both in optimal concentrations; it also contains stabilized bovine plasma, completely free of the 4 factors to be determined, and calcium in optimal concentration. The dehydrated and vacuum-sealed reagent will keep at least 12 months, and the activity is unchanged after 30 days' storage at 47 C. In solution and ready for use, the activity is constant for at least 12 hours at room temperature. The method has been worked out for capillary blood, citrate venous blood, and citrate plasma, and only 0.10 ml. of blood is needed. The test is quickly and easily performed.

BOOK REVIEWS

Preventive Medicine: Principles of Prevention in the Occurrence and Progression of Disease. Edited by Herman E. Hilleboe, M.D., Commissioner of Health, State of New York, Department of Health, Albany, and Granville W. Larimore, M.D., Deputy Commissioner of Health, State of New York. Cloth. $12. Pp. 731, with 59 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5; 7 Grape St., Shaftesbury Ave., London, W. C. 2, England, 1959.

According to its preface this volume sets forth a new way to look at preventive medicine and is intended for medical students, general practitioners, specialists, and workers in health agencies. It endeavors, through the contributions of 29 experts, to discuss the prevention of disease and to show how a disease, once established, may be managed in its further progress.

Early diagnosis is often impossible because the patient insists on self-medication for the complaint at hand. Then, when it gets beyond relief, he seeks medical advice—often too late. Advances in preventive medicine continue to be publicized in both the medical and the lay press. This is all to the good; for the high hope is that much disease can be prevented if patients, or the public in general, become fairly well acquainted with symptoms which will lead to consultation with doctors of medicine. Unfortunately, this is too often wishful thinking. Further than that, it is sometimes questionable whether we have not overextended ourselves, thus unwittingly establishing a fear complex leading to anxiety and neuroses which are not based on fact. This is an undesirable by-product which is seemingly unavoidable. On the whole, a knowledge of prevention of both accidents and disease is highly desirable; it is a question of the greatest good for the greatest number.

Much of the material in this book has been set forth in magazines, pamphlets, and public lectures. Publicity concerning the newer remedies is so well distributed that a patient may confound his physician with news of some remedy that was too highly praised in the morning paper. Neither doctor nor patient can know everything about everything.

In general the authorities who have contributed special articles to this volume write from experience, but it might have been just as well to limit the discussion to prevention and to have omitted part 2 which deals with prevention of progression. Another and different volume might well be written on this phase. For the physician who wishes to learn how to halt a chronic or well-established condition, there is still much to be discovered. In part 2 the editors of this volume have limited themselves to a discussion of periodic health inventories, cancer detection and screening, and have done the same for pulmonary tuberculosis, heart disease, diabetes mellitus, and hearing and visual defects. In section C there is a follow-up of such screening and diagnostic examinations, and other sections deal with rehabilitation, alcoholism, and narcotic addiction. Part 3 is devoted to health education for the public and postgraduate studies for the physician. There are chapters on social work, public health nursing, the role of the hospital, epidemiologic methods and inference, and a final chapter on official and voluntary health agencies. This book attempts to cover too much ground and in too sketchy a manner. For the most part it is written in a fluent style, without disturbing and difficult technicalities. This makes for easy reading by nonmedical persons as well as the medical profession.

Staphylococcus Pyogenes and Its Relation to Disease. By Stephen D. Elek, M.D., D.Sc., Ph.D., Professor of Bacteriology in University of London, London. Cloth. $15. Pp. 767, with 45 illustrations. Williams & Wilkins Company, 428 E. Preston St., Baltimore 2; E. & S. Livingstone, Ltd., 16 and 17 Teviot Pl., Edinburgh 1, Scotland, 1959.

Professor Elek's new book is written for scholars in the field of bacteriology. It is not a compendium of information of general interest to clinicians. On the other hand, it should be read with great care by any clinician to whom the responsibility for staphylococcic infections has been given. The most unusual and complete bibliography, which comprises some 188 pages of the volume, is well worth the cost of the book. The sections entitled Historical Survey and Problems of Taxonomy are written as only an expert could write them. In the field of metabolism of staphylococci the volume leaves something to be desired if it is viewed by a biochemist or microbiologist with particular leanings toward chemistry. A clear elucidation of the status of knowledge concerning phage, lytic phenomena, and coagulase reactions is given. The peculiar relationships between virulence and the simple presence of organisms which could be virulent in the environment of man are stressed and described. Many features of this aspect of staphylococci and their behavior remain to be clearly described. Chapter 14, which deals with antibiotics, gives a superb account of the historical aspects of the development of antibiotics, the mode of their action, the situation with regard to antibiotic-resistant strains of staphylococci, and specific considerations of other antibiotic substances. Such a book should be a welcome addition to a good medical library at any time. Coming at a time when there is an international problem of antibiotic-resistant staphylococci that have apparently increasing virulence for man, the book stands alone as a guide to this entire subject.

These book reviews have been prepared by competent authorities but do not represent the opinions of any medical or other organization unless specifically so stated.

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QUESTIONS AND ANSWERS

DETERMINATION OF PARENTAGE

To the Editor:—*When a child's mother is missing, are there tests, blood or other, which could prove or disprove parentage of a man suspected of being the father?*

M. A. Shillington, M.D., Brainerd, Minn.

Answer.—In disputed paternity proceedings, blood grouping determinations offer a reliable scientific means of solving the question in many cases. Paternity can never be proved by means of blood tests. However, nonpaternity can be proved in a considerable proportion of the cases by an accurate analysis and comparison of the four main groups and the various subgroups of the child, mother, and alleged father. Even in the absence of the mother, in some cases it is possible to prove nonpaternity. For example, a man belonging to group AB cannot be the father of a child with group O and a man with group O blood cannot be the parent of a child with group AB. Also, a man with type M cannot be the father of a child with type N, nor can a man with type N have a child with type M. Such determination should be conducted only by a serologic laboratory that is constantly doing this type of work and in which there are adequate facilities for checking and rechecking the serums used and the results obtained.

AMEBIC DYSENTERY PROPHYLAXIS

To the Editor:—*If one goes to an area where the incidence of amebic dysentery is high, what is the effectiveness of using an amebicide, such as glycobiarsol, prophylactically? Does such medication prevent clinical infection or does it merely suppress symptoms? What is the adult and child's dosage schedule, and over how long a period can it be used?*

Fordyce L. Howe, M.D., Fort Wayne, Ind.

Answer.—Chemoprophylactic investigations by Beaver (*Am. J. Trop. Med.* 5:1015, 1956) showed that the daily administration of 250 mg. of glycobiarsol not only protected against infection with Entamoeba histolytica but also terminated infection in infected controls. Sanchez Vegas (*J. A. M. A.* 151:1059-1065 [March 28] 1953) administered glycobiarsol to 87 persons suffering from intestinal amebiasis. He used larger doses than are currently recommended (1 Gm. three times daily, after meals, for 35 days). Some of his patients received as much as 200 Gm. of glycobiarsol during the entire course of treatment. Of 87 patients given these large doses, 2 complained of headache and transitory urticaria, 16 of pruritus ani, 26 of flatulence, and 28 of indigestion. Glycobiarsol can be used effectively in the prophylaxis and treatment of amebiasis, and it can be used over a long period provided the person is not allergic to arsenicals or bismuth. The recommended prophylactic dose is one tablet (250 mg.) once daily for children over 10 years of age and adults and one-half tablet once daily for children under 10.

The inquirer made no mention of the country to be visited. If malaria is also endemic in the area, glycobiarsol-chloroquine phosphate combination tablets would be the agent of choice, for they would not only protect against malaria and intestinal amebiasis (Berberian and others, *J. A. M. A.* 148:700-704 [March 1] 1952) but also prevent systemic dissemination and extraintestinal localization of amebas. Each tablet contains 250 mg. of glycobiarsol and 75 mg. of chloroquine. The prophylactic dose would be one tablet per diem for adults and one-half tablet for children.

UNILATERAL KIDNEY CYST

To the Editor:—*Should asymptomatic unilateral cyst of kidney be treated surgically? If so, should nephrectomy, heminephrectomy, or cyst excision be done?* *W. S. Levy, M.D., Woonsocket, R. I.*

Answer.—In general, asymptomatic unilateral cyst of the kidney should be treated surgically. The reason for this is the difficulty in positively excluding a malignancy of the kidney in the differential diagnosis. Aortography has been suggested as a means of making this differential diagnosis, but this it not always satisfactory. Needle biopsies have also been done on patients of advanced age in an effort to settle the diagnosis. If the fluid obtained is clear and straw colored, there is some assurance that a cyst is present. However, in most instances, surgical exploration in the flank area, with exposure of the kidney, can be carried out with minimal risk and a more accurate evaluation obtained. If the cyst is found to be very large and has compressed or destroyed a fair portion of the kidney, nephrectomy is the procedure of choice. If, however, an appreciable amount of functioning renal tissue remains, incision of the cyst with close inspection of the point of attachment to the renal parenchyma is indicated. Many times in the base of the cyst there is a confluence of blood vessels with proliferative tissue

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changes, sometimes suggesting an underlying malignancy. If there is any question of this, nephrectomy is indicated. However, malignancy within a renal cyst is uncommon. If the cyst seems to be definitely benign, its excision close to the margin of the renal parenchyma, with suture of the cyst edge to the adjacent renal parenchyma with a superficial mattress suture, is indicated. If there is any question of the edges of the cyst approaching one another it is well to pack the cavity with iodoform gauze for a period of time. If it seems advisable to remove the base of the cyst from the renal parenchyma, it is better to carry out partial nephrectomy, keeping the incision line at least a centimeter away from the base of the cyst. This will avoid extensive bleeding in many instances.

SUPERFICIAL PUNCTATE KERATITIS

To the Editor:—*What is considered the most effective treatment for superficial punctate keratitis? This case has persisted for six months and has shown no improvement with chloramphenicol eye drops and sulfacetamide sodium. Does the latter retard healing of corneal epithelium? Is there any danger from an infra-red heat lamp used for five minutes several times each day over a long period of time? Would Microtherm therapy help, or would it be contraindicated? Several cultures and smears are negative.*

M.D., North Carolina.

Answer.—Superficial punctate keratitis is considered to be due to a virus infection. At present, there is no known treatment for this condition that can be used with assurance of success. Chlortetracycline and chloramphenicol as eye drops are considered the most effective local antibiotics. Cauterization of the corneal epithelium with weak iodine solution or ether is effective in many cases. More drastic treatment would be to denude the corneal epithelium with forceps or by scraping, and then cauterize with iodine or ether. The eye is then bandaged. Potassium iodide in a 2% solution as eye drops has been used with benefit. The oral use of sodium iodide solution, giving 1 grain (65 mg.) per 10 lb. of body weight three times daily for 10 to 14 days, is helpful if started early. The corticosteriod drugs given locally or systemically are contraindicated. Cold compresses to the eye may afford relief. Sulfacetamide sodium as an ointment may retard corneal epithelial healing, as many ointment bases will do. In drop form, the drug is not known to retard healing. Use of infra-red or any form of heat is contraindicated because it is believed that viruses thrive on mild heat. Microtherm therapy is contraindicated on the same premise. It is not uncommon to overtreat a case such as this, and if all else fails treatment might be stopped entirely except for the use of an eye wash of isotonic sodium chloride solution.

EFFECTS OF "HOT ROAD OIL"

To the Editor:—*A state insurance fund has asked whether hepatitis in an employee may have been due to breathing smoke from "hot road oil" used in patching asphalt roads. This mixture consists of asphalt, tar, and possibly some other ingredients which are heated to high temperatures with butane or kerosene. Since this material is used widely throughout the United States and no report has been seen of a resulting hepatitis, the etiological implications are questionable. However, so that no injustice is done to the patient, please give further information. There have been no hematological or neurological changes, and the patient has fully recovered. The inhalation occurred over a period of six months or more.*

R. P. Howard, M.D., Pocatello, Idaho.

Answer.—As the inquirer states, thousands of road workers using asphalt follow daily practices that are much the same over the entire United States. The chemicals are nearly the same, and likewise the fuels. Moreover, this type of work has been going on for about 50 years. If hepatitis was an expectable result of exposure it would have attracted medical attention long ago. Such is not the case. What may be indicated here is exploration of the method of skin clearing after work. After the workman is left to his own devices he may use almost any chemical detergent. If this workman resorted to use of a solvent such as carbon tetrachloride, even in small amounts and for brief periods, the occurrence of chemical hepatitis is plausible.

PREGNANCY AND KERATOCONUS

To the Editor:—*A woman with keratoconus has had three successful pregnancies. During each pregnancy, there was deterioration of visual acuity which was brought up to 20/30 or better by a change in glasses. She is pregnant again, and the question has been raised whether therapeutic abortion and sterilization is justified.*

Raymond S. Goux, M.D., Detroit.

Answer.—Keratoconus, or conical cornea, is a noninflammatory condition of the cornea which may be either rapidly or slowly progressive. It is more common in females and in some cases may be hereditary, though this is by no means common. The consensus is that there is some relationship between the development of conical cornea and the endocrine system. Therefore, it is natural to expect the condition to become worse after each pregnancy. However, as most cases of conical cornea progress over a period of years, it is a matter for individual decision as to whether pregnancy should be interrupted. If the change has been of 3 or 4 D. each time, one would feel justified in advising therapeutic abortion. In other words, if one can be sure that pregnancy definitely aggravates the condition

to a marked degree, abortion and sterilization should be performed. Corneal transplantation will arrest keratoconus to a marked degree and restore the patient's vision to nearly normal provided operation is performed when the condition is not too far advanced.

ELBOW DISLOCATION IN A CHILD

To the Editor:—*Children under 2 or 3 years of age who have dislocated an elbow have often been seen. Treatment has included reduction as an office procedure, without use of x-rays. Is this a risk, from the viewpoint of malpractice? The whole procedure has seemed so simple that additional treatment appears unnecessary.*

M.D., Massachusetts.

Answer.—Dislocation of the elbow in a child of 2 or 3 years is quite unusual. On the other hand, the so-called luxation of the head of the radius in relation to the annular ligament is quite common. The area is maintained in pronation, and any attempt at motion is quite painful. This luxation can be readily reduced by supinating the hand. It would seem likely that this is what is meant in the question. True dislocation of the elbow is of such importance that x-rays ought to be taken. Dislocation may be associated with other injury, such as displacement of the medial condylar epiphysis, which x-ray would show. If it is difficult to obtain an x-ray immediately and the child shows undoubted symptoms of dislocation of the elbow, general traction followed by bringing forward the distal unit with flexion may be carried out to see if reduction may be accomplished. One must depend greatly on traction. Manipulation must be done most judiciously. X-rays should be taken afterward to be sure the epiphyses are in proper position.

ALUMINUM INHALATION THERAPY

To the Editor:—*What is the present medical opinion regarding efficacy of aluminum inhalation therapy for prevention and treatment of silicosis in the sanitary pottery industry?*

D. C. Simmons, M.D., Kilgore, Texas.

Answer.—Present opinion on the therapeutic and prophylactic use of aluminum inhalations with silicosis still is somewhat divided. A statement which seems to represent the thinking of most authorities on the subject can be found in the book by Patty entitled "Industrial Hygiene and Toxicology" (New York, Interscience Publishers, Inc., 1958, vol. 1, pp. 394-397). The statement is made that all possible methods of preventing silica dust dissemination in the working atmosphere must be used before considering aluminum dusting. It is recognized that satisfactory engineering control of dust in the pottery industry is difficult to achieve, especially when the content of crystalline-free silica in the clay is high. If silicosis still develops among workers in spite of the best kind of dust control available, then the use of aluminum inhalation may be justifiable on a preventive basis only. Its use in treatment of an already-established case of silicosis cannot be justified, however, except on a purely psychological basis.

CARDIAC PACEMAKER

To the Editor:—*A cardiac pacemaker and a cardioscope have been acquired in the local hospital. There has been considerable controversy as to proper use in cardiac conditions other than the asystole encountered during anesthesia. Will attaching the cardiac pacemaker to a normal person for demonstration purposes entail any danger to the subject? Is the cardiac pacemaker of any value in treating extrasystoles, paroxysmal tachycardia, auricular flutter, auricular fibrillation, or any nodal or idioventricular arrhythmia?*

Robert L. Salb, M.D., Crossett, Ark.

Answer.—It is probably not advisable to attach the cardiac pacemaker to a normal person. The cardiac pacemaker might interrupt the subject's normal cardiac rhythm, and this could be dangerous. Thus far, it has not been proved that the cardiac pacemaker is of any value in the treatment of extrasystoles, paroxysmal tachycardia, auricular flutter, auricular fibrillation, or nodal or supraventricular arrhythmia.

THROMBOEMBOLIC EPISODES

To the Editor:—*Is there any evidence that administration of diuretics, as for congestive heart failure, predisposes to or tends to precipitate thromboembolic episodes, especially in cerebral vessels?* *Collin Baker, M.D., Tampa, Fla.*

Answer.—It has not been shown that administration of diuretics to patients with congestive heart failure in any way predisposes or causes thromboembolic episodes. It was once thought by a few workers that administration of digitalis to patients with congestive heart failure predisposed to such episodes, but this too has been definitely proved untrue.

LOSS OF SKIN PIGMENT

To the Editor:—*Please give information concerning development of vitiligo, secondary to a rash, in a person who processes the plastic Bakelite.*

Robert C. Puestow, M.D., Manitowoc, Wis.

Answer.—Loss of pigment after an inflammation such as a dermatitis is properly called a leukoderma. It is usually temporary. A condition resembling vitiligo may be observed after exposure to monobenzylether of hydroquinone. This antioxidant is

found in rubber. The mechanism is an actual inhibition of melanin formation. It has also been found that hydroquinone and p-hydroxypropiophenone are effective inhibitors of mammalian melanin formation. So far as is known, these chemicals are not encountered in the manufacture of Bakelite.

WAX AS CARCINOGENIC FACTOR

To the Editor:—*The question has been asked whether the wax coating on the inside of milk cartons may be carcinogenic, since it has been reported to have produced carcinoma in mice. Might it be a contributing factor in carcinoma of the bladder or elsewhere?*

M.D., West Virginia.

Answer.—Development of papillomas in the bladders of rats after implantation of paraffin pellets has been reported by Bonser. In another unreported but verified study, implantation of paraffin pellets in the bladders of mice resulted in papillomas and cancers. While the majority of commercial waxes are apparently free of significant amounts of known carcinogenic impurities, several have been demonstrated to contain dibenzanthracene. This may be released into milk. The American Petroleum Institute, at the instigation of the Milk Industry Foundation and other interested groups, has been conducting research on this problem (*News Letter* of the Milk Industry Foundation, March 30, 1959).

ATOPIC DERMATITIS AND CLIMATE

To the Editor:—*In* The Journal, *Jan. 17, 1959, page 306, in Questions and Answers, a question was raised about atopic dermatitis and climate. The consultant's discussion of the climate factor was quite good. In his opening remarks, he mentioned the possibility of the development of other manifestations of atopy and in his concluding remarks, the financial burden and family disarrangement involved. It seems to me that he could have mentioned that a complete allergic survey and good allergic management would be a more rational approach in such a case.*

Edward Pickert, M.D.
679 Irvington Ave.
Newark 6, N. J.

The above comment was referred to the consultant who answered the original question, and his reply follows.—Ed.

To the Editor:—*The question originally asked was specifically in respect to the relief of atopic dermatitis which might be achieved by climatologic therapy. In a short reply, it was not possible to present all the methods of management which have varying effects in this difficult clinical syndrome. Allergic management is one of these, though it, like all other methods of treatment, fails in many cases. It is the opinion of this consultant that chief emphasis in respect to an allergic component should be placed on a carefully taken history and observation of the patient, in respect to exacerbations which might be attributable to clinical exposure to various ingestant and inhalant allergens. Unfortunately, allergic management based primarily on the results of scratch and intradermal tests and on attempts at hyposensitization and procedures is infrequently effective and sometimes harmful. It is characteristic of atopic dermatitis that there are multiple reactions to a wide variety of scratch tests and that there is often no relation of the specific positive tests to the dermatitis. There is considerable controversy on this matter, some of it quite vehement, but it can be confidently stated that the conditions of too many patients with atopic dermatitis are managed routinely on this basis with little likelihood of benefit. If scratch and intradermal tests are carried out, the relation of specific positive reactions to the dermatitis should be confirmed or disproved clinically if at all possible. It is unwise to restrict the patient's environmental contacts, or his diet, or to undertake interminable courses of "hyposensitizing" injections unless some good is likely to result therefrom.*

WEIGHT GAIN AFTER CESSATION OF SMOKING

To the Editor:—*The answer to Dr. Trapnell's question on weight gain after stopping smoking (*J. A. M. A. *169:1269 [March 14] 1959) implies that ingested calories are absorbed from the intestine at the same rate whether one smokes or not. Could you supply confirmatory data?*

Armistead D. Williams, M.D.
The Chesapeake and Ohio Hospital
Clifton Forge, Va.

The above comment was referred to the consultant who answered the original question, and his reply follows.—Ed.

To the Editor:—*A survey of the current literature and contemporary textbooks on pharmacology and physiology reveals no reference to any alteration of absorption effected by smoking and/or nicotine.*